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THE UNIVERSITY OF ALBERTA

ORGANIC SYNTHESES VIA ENOL BORINATES

by

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A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

IN CHEMISTRY

EDMONTON, ALBERTA
FALL, 1979

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

Organic Syntheses via Enol Borinates

submitted by Jan Oudenes in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry.

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Date Oct. 4, 1979

Aan mijn vader, voor mijn moeder

ABSTRACT

The structure of terminal enol borinates derived from the reaction of α-diazo ketones with dicyclohexylborane was established by ^{1}H and ^{13}C NMR spectroscopy. These enol derivatives react regiospecifically with aldehydes and ketones to give β-trimethylsilyloxy ketones upon treatment with N-trimethylsilylimidazole. The by-product (1-imidazolyl)dicyclohexylborane was shown to have a polymeric structure 26.

Enol borinates were also convenient precursors for the synthesis of α,α'-di-aldol condensation products. Diazoacetone was reacted with triethylborane followed by addition of an aldehyde to give an intermediate β-dialkylboryloxy ketone, which was subjected to kinetic deprotonation with lithium diisopropylamide and treatment with a second aldehyde, resulting in β,β'-dihydroxy ketones upon hydrolysis. This reaction occurred regiospecifically as was shown by the synthesis of several isomeric sets of di-aldols via this procedure.

A general route for the preparation of centrally unsubstituted and monosubstituted β-diketones was developed. Treatment of enol borinates with nitriles led to the formation of 1H-boroxazines which could be conveniently hydrolyzed to the corresponding β-diketones.

It was shown that enol borinates could be regio-

specifically alkylated with simple alkyl halides in the presence of a suitable, "activating" nucleophile.

Finally, it was discovered that the reaction of α-diazo ketones and trialkylboranes led stereospecifically to the thermodynamically less stable E-type enol borinates. These enol derivatives were converted to the corresponding enol trimethylsilyl ethers without loss of stereospecificity upon treatment with N-trimethylsilylimidazole.

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CHAPTER I

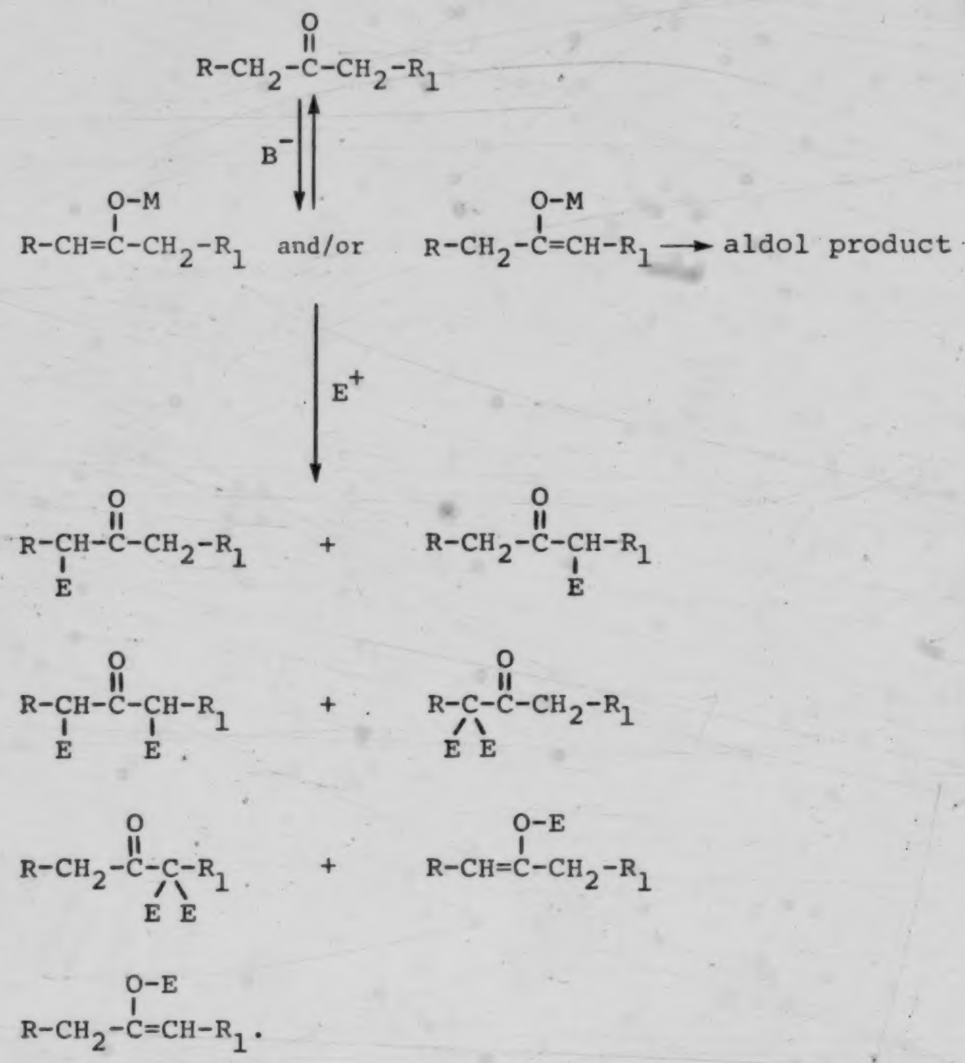
INTRODUCTION

Part A. The Regiospecific Preparation of Ketone Enolates.

The construction of carbon-carbon bonds is vital in the synthesis of organic molecules, and reactions which involve carbanion or "carbanion-like" intermediates are most frequently employed for this purpose. The carbonyl group is often used (Wittig, Grignard, Michael, aldol condensation reactions, among others), since the α-hydrogens are quite acidic (pK ~ 20) and can be readily removed by a variety of bases to prepare the corresponding metal enolates. These nucleophilic species in turn are quite suitable to participate in aldol condensation, alkylation, Mannich and other reactions.

The ease with which these reactions occur would make it an attractive route for the construction of new carbon skeletons. Unfortunately, the utilization of this synthetic scheme is seriously hampered by a number of problems as is outlined in Scheme I. The alkylation of carbonyl compounds can be subdivided into two processes, requiring: (a) the abstraction of an α-proton, and (b) the subsequent introduction of an electrophile to the newly formed enolate. However,

SCHEME I


B⁻
and/or
aldol product
E⁺

there are complications in both steps that can result in the failure of a successful ketone alkylation.

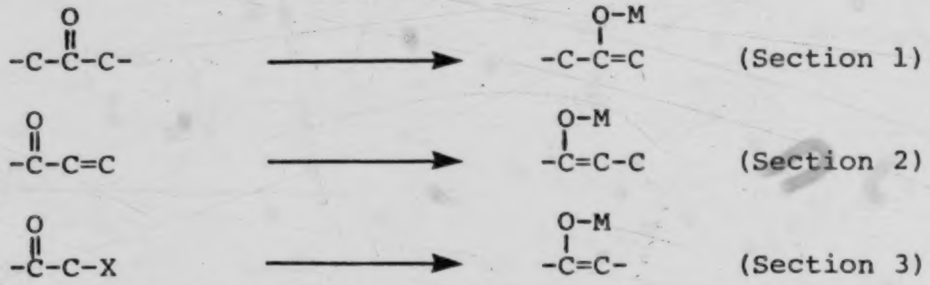
In the case of unsymmetric ketones, competing proton transfer reactions often complicate the formation of site-specific enolates. Ketones can also undergo extensive self-condensation during the proton abstraction step, but this varies widely with the structure of the carbonyl compound. For example, cyclopentanone is much more prone to undergo self-condensation than cyclohexanone[1].

The alkylation step can also result in side reactions due to proton transfer (and thus loss of regiospecificity), which in turn can give rise to competitive aldol condensations and polyalkylation products. In addition, the ambident nature of a metal enolate sometimes leads to O- rather than C-alkylation, depending on structure, cation, and solvent system[2].

Since the vast chemistry of enolates and enol derivatives has already been reviewed by Conia[1], House[2], d'Angelo[3], Jung[4], and Jackman and Lange[5], only certain selective approaches will be presented here towards the regioselective generation of enolates and their derivatives (part A). The alkylation of these species will be discussed in part B of this chapter.

Enol(ate) Generation. This can be accomplished in a variety of ways, but it is possible to classify them into three general methods as illustrated in Scheme II: (1) direct deprotonation of carbonyl compounds, (2) "dissolving metal" reduction of enones and conjugate addition of nucleophilic species to enones, and (3) a variety of reactions of ketones that involve (formal) displacement of an activating substituent at the α-position. A brief summary of each of these categories follows in Section 1, 2 and 3.

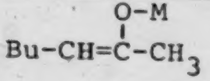
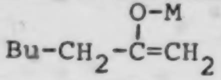
Scheme II

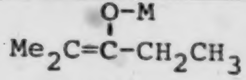
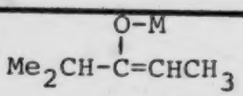


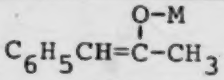
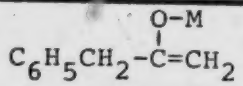
1. Direct Deprotonation of Carbonyl Compounds.

a. Thermodynamically Controlled. The most direct route to enolates is via treatment of ketones and other enolizable carbonyl compounds with sufficiently strong bases. They are frequently analyzed by quenching with D_2O (or deuterioacetic acid)[6], acetic anhydride[6], and chlorotrimethylsilane[7,8,9]. However, metal enolates

Table I. Ratio of Positional Isomers for Metal Enolates and Enol Derivatives under Equilibrium and Kinetically Controlled Conditions[a]

M	 $Bu\text{-}CH{=}\overset{O\text{-}M}{\overset{\vert}{C}}\text{-}CH_3$ (%)	 $Bu\text{-}CH_2\text{-}\overset{O\text{-}M}{\overset{\vert}{C}}{=}CH_2$ (%)	mode
K	58	42	Equil.
Li[b]	ca. 87	ca. 13	"
Ac	97	3	"
Me_3Si	87	13	"
K	46	54	Kinetic
Li	16	84	"

M	 $Me_2C{=}\overset{O\text{-}M}{\overset{\vert}{C}}\text{-}CH_2CH_3$ (%)	 $Me_2CH\text{-}\overset{O\text{-}M}{\overset{\vert}{C}}{=}CHCH_3$ (%)	mode
K	12	88	Equil.
Li	1	99	"
Ac	55	45	"
Me_3Si	18	82	"
Et	55	45	"
Li	5	95	Kinetic

M	 $C_6H_5CH{=}\overset{O\text{-}M}{\overset{\vert}{C}}\text{-}CH_3$ (%)	 $C_6H_5CH_2\text{-}\overset{O\text{-}M}{\overset{\vert}{C}}{=}CH_2$ (%)	mode
K	~100	~0	Equil.
Li	~100	~0	Kinetic
Me_3Si	~100	~0	Equil.

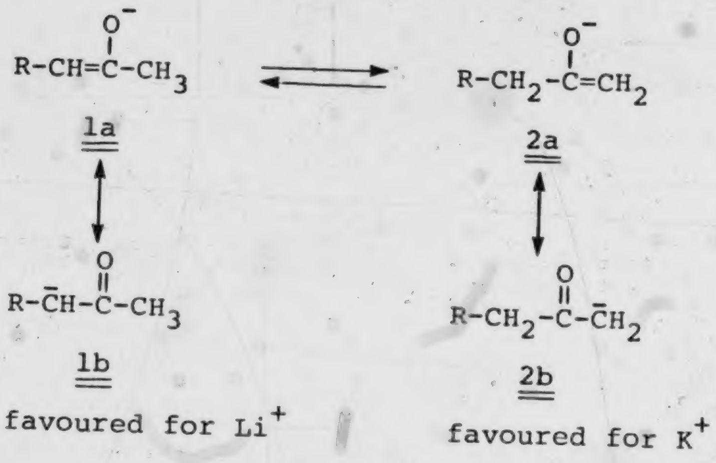
[a] Reference 6, 9 and 10.

[b] These results are not accurate due to extensive self-condensation.

equilibrate very rapidly in the presence of proton donors, producing equilibrium mixtures of positional isomers. House and coworkers[6], for example, treated a small excess of a mixture of 4-methyl-2-pentanone and α,α'-pentadeuterio-4-methyl-2-pentanone with triphenylmethylpotassium and observed that the deuterium label was completely scrambled within 15 minutes at room temperature. This technique is used to form equilibrium mixtures of metal enolates[6,9,10] and the ratio of positional isomers for several representative ketone enolates is shown in Table I.

It can be seen from these data and other examples[2] that the difference in energy between the isomeric enolates of ketones is usually very small. In general, the more substituted isomeric enolate possesses a higher stability (1 > 2), which has been attributed to hyperconjugation by the α-alkyl substituents[2]. This is especially true for metal enolates with a more covalent character (e.g. Li). Changing the metal cation from lithium to potassium shifts the equilibrium towards the less highly substituted enolate ion (Scheme III). This has been explained in terms of the more ionic character of the potassium-oxygen bond which would cause the "carbanion-like" resonance structures (1b and 2b) to become relatively more important. Hence, the less highly substituted enolate 2 would be favoured in

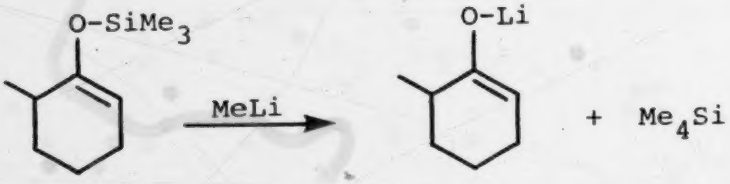
Scheme III



this case because alkyl substituents destabilize "carbanion type" resonance structure 1b (relative to 2b) due to electrostatic reasons.

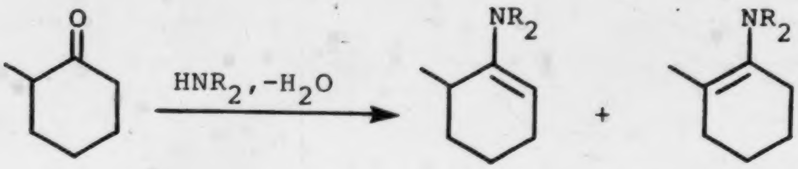
1.b. *Kinetic Deprotonations*. The less stable enolate can often be formed predominantly by using the technique of "kinetic deprotonation". The ketone is slowly added to an excess of strong base (lithium diisopropylamide and other "hindered bases" are often employed) and precautions are taken that base is present in excess throughout the addition. Equilibration is now reduced since there is never a proton donating source available during the reaction. Equilibration can nevertheless occur during a finite period of mixing as is exemplified in the "kinetically" and thermodynamically controlled enolization of 1-phenyl-2-propanone[6,9]. The rate of isomerization appears to increase when potassium rather than lithium is employed[6,9], presumably due to the more ionic character of the former species.

Although the regiospecific generation of metal enolates by means of strong bases is limited, it is nevertheless possible to quench these species with chlorotrimethylsilane or acetic anhydride to form stable enol derivatives. These ethers and acetates are then purified by physical separation techniques (e.g. preparative gas chromatography)[7-9]. Each individual regioisomeric enolate can then be regenerated by reaction with methyllithium. Enol silyl ethers are particularly useful in this respect since the by-product tetramethylsilane, is unreactive (eq. 1).



(1)

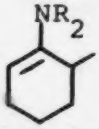
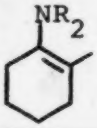
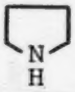
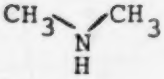
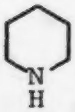
1.c. Masked Enol Derivatives. Several indirect approaches have been developed to circumvent the problems which are normally encountered in the direct generation of regioselective enolates. Enamines, for example, are widely used as masked enolates[11] (eq. 2). Their importance results chiefly from the fact that the less



(2)

highly substituted enamine is generally the predominant product, although the ratio of positional isomers[12] is dependent on the secondary amine used in the synthesis of such compounds (Table II). For example, reaction

Table II. Ratio of Positional Isomers for Enamine Derivatives of 2-Methylcyclohexanone (Eq. 2)[a]

	%, enamine of 2-methylcyclohexanone[b]	
amine		
	90	10
 CH_3NHCH_3	60	40
	46	54

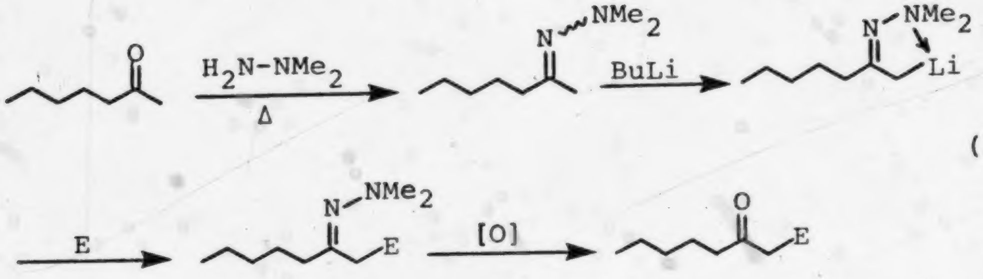
[a] Reference 12.

[b] Equilibrium values.

of 2-methylcyclohexanone with pyrrolidine in the presence of an acid catalyst resulted in a 90:10 equilibrium mixture of positional isomers in favour of the less substituted enamine. Table II shows, however, that this ratio can change rather dramatically when other secondary amines (e.g. dimethylamine, piperidine) are employed in the generation of these compounds.[12].

Metallated imines[13,14] and oximes[15] are also utilized as masked enol(ate) derivatives but all of these methods suffer to a certain degree from the fact that the formation and hydrolysis of these compounds consist of two different steps, at times giving rise to complications.

Stork and coworkers[14] also introduced N,N-dialkylhydrazones for the purpose of accomplishing a clean alkylation and this synthetic method was later developed



(3)

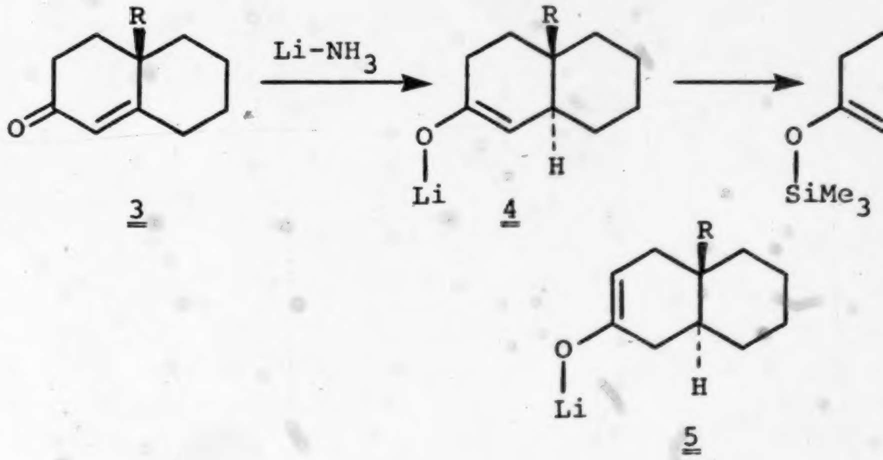
into a potentially useful method by Corey and Enders[16]. The latter workers showed that proton abstraction occurs generally regiospecifically at the less highly substituted carbon (eq. 3). These hydrazones could be easily formed by the reaction of ketones (or other carbonyl compounds) and N,N-dimethylhydrazone and, importantly, it was found that removal of the masking moiety could be smoothly performed with buffered sodium periodate.

2. Enol(ate) Formation from Conjugate Addition of Nucleophiles to Enones and Cyclopropyl Ketones.

Although direct deprotonation of ketones usually results in a mixture of regioisomeric enolates, it is nonetheless possible to generate these derivatives in a regiospecific manner. One way to accomplish this is by the addition of nucleophiles (e.g. cuprates) to enones or, sometimes, cyclopropyl ketones. A number of these methods will be briefly discussed in this Section.

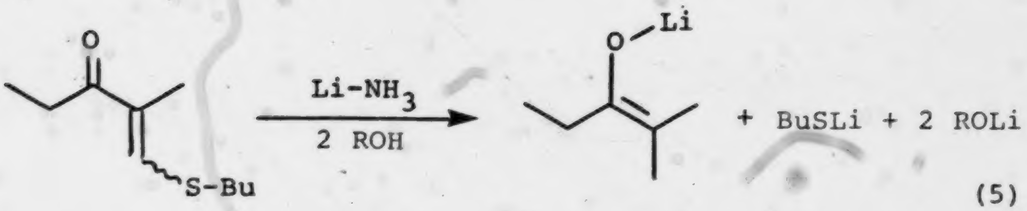
2.a. "Dissolving Metal Reduction". The reduction of enones in the presence of lithium in liquid ammonia leads to site-specific[17-19] enolates, in which an enone formally undergoes a conjugate addition by a hydride nucleophile. This particular application of a "dissolving metal reduction" was initially developed by Stork[17] in the octalone series and by Weiss and coworkers[18] in the field of steroids at approximately the same time.

The positional isomers 4 and 5 (R = H, eq. 4) are formed in an equilibrium ratio[10] of roughly 50:50, while 5 is readily available in a 90:10 ratio (of 5:4) under conditions of kinetic control.[10,20] Nevertheless, enolate 4 was found to be the sole isomer when octalone 3 was reduced with lithium in liquid ammonia (as shown by trapping with reactive electrophiles[17,21,22], e.g. chlorotrimethylsilane).



(4)

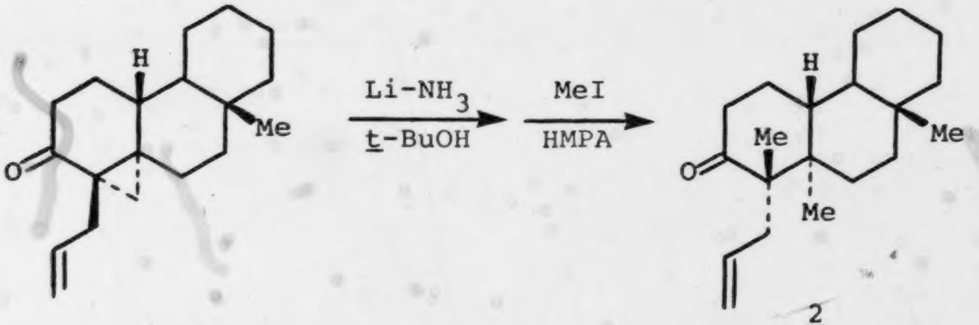
It has also been reported that certain enolates can be constructed from butylthiomethylene derivatives *via* reduction with lithium in liquid ammonia. For example, the more highly substituted lithium enolate of 2-methyl-3-pentanone was prepared in this manner from 2-butylthiomethylene-3-pentanone (eq. 5)[23]. The reaction must involve a simultaneous reduction of the carbon-sulfur bond and the enone. It is of interest



(5)

to note that the less highly substituted enolate is available by thermodynamic equilibration in 99% regioisomeric purity (see Table I)[6,10].

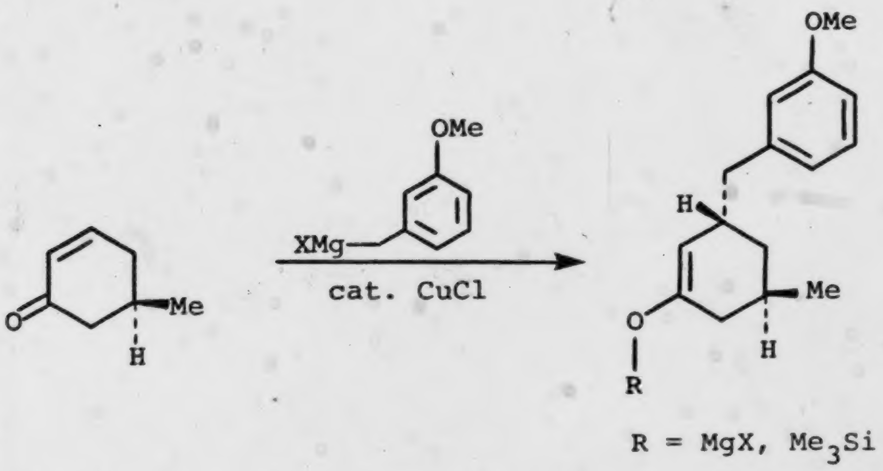
2.b. Cyclopropyl Ketones. These ketones have also been shown to undergo a similar reductive cleavage with lithium in liquid ammonia producing regiospecific enolates[24,25]. A major synthetic challenge in the synthesis of lupeol was the introduction of two vicinal methyl groups in ketone 2 with the correct trans stereochemistry[25]. It was found that this transformation could be conveniently accomplished in good yield by application of a "dissolving metal reduction" followed by methylation of the formed enolate (eq. 6).



2

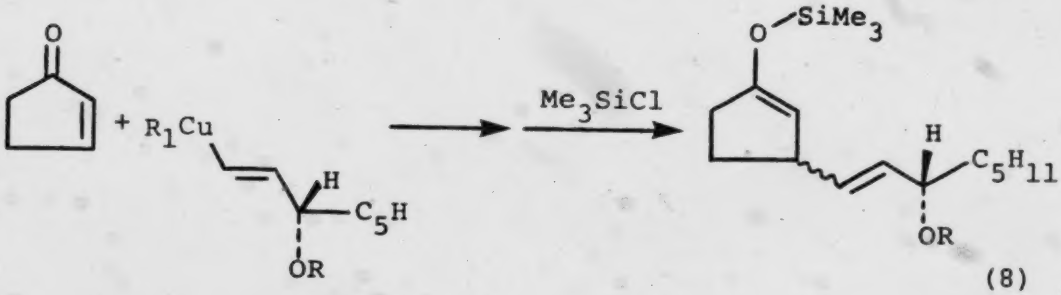
(6)

2.c. Grignard Reagents. The copper-catalyzed 1,4-addition of Grignard reagent to enones has been frequently used to yield β-alkylated ketones upon hydrolysis. These reactions provide, of course, an easy access to regiospecific halomagnesium enolates, which can be trapped and purified as their enol silyl ethers[26-31]. Stork applied this concept elegantly in the synthesis of lycopodine (eq. 7), thus simultaneously accomplishing the stereoselective introduction of an alkyl chain and the regiospecific formation of an enol(ate), which was used in the further elaboration of the carbon skeleton[26].



(7)

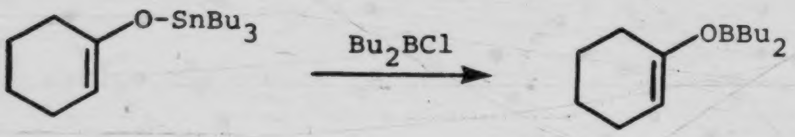
2.d. Cuprate Addition. Lithium dialkylcuprates have also been extensively used in the generation of regiospecific metal enolates[32-44]. They may be isolated as their enol silyl ether derivatives or employed *in situ* in subsequent reactions with reactive carbon electrophiles. This methodology has been of specific value in synthetic approaches to prostaglandins[38-42]. For example, reaction of an optically active lithium dialkylcuprate with cyclopentenone produced, after silylation, a regioisomerically pure enol silyl ether (eq. 8), which could be subsequently used for the synthesis of a prostaglandin[38].



(8)

2.e. Enol Borinates. The development of organoborane and aluminum compounds in recent years has become of considerable interest in organic chemistry and several routes have been explored to form enol borinates and aluminum enolates. A Russian group reported that the tin enolate of cyclohexanone could be converted to the corresponding enol borinate in the presence of chlorodibutylborane[45] as illustrated in equation 9.

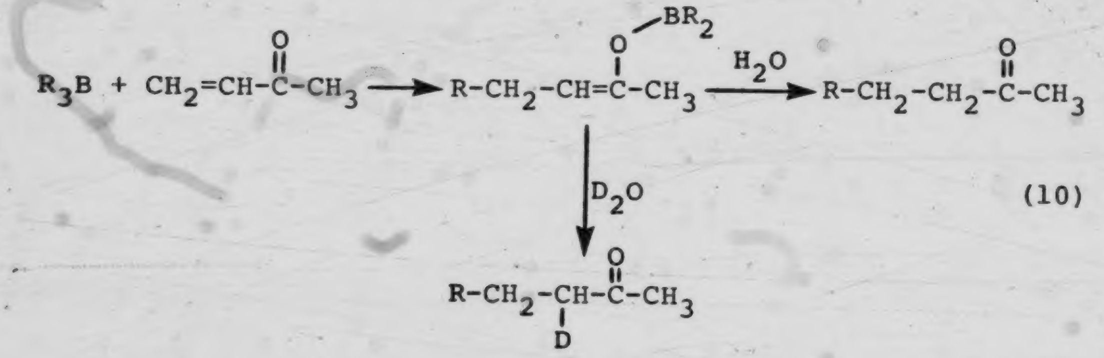
Brown, Suzuki, and their respective coworkers[46,47]



(9)

discovered that trialkylboranes react readily with α,β-unsaturated carbonyl compounds in the presence of catalytic amounts of radical initiators to give aldehydes and ketones after hydrolysis.

For example, treatment of tributylborane with methyl vinyl ketone resulted in the formation of 2-octanone upon hydrolysis as shown in equation 10. It

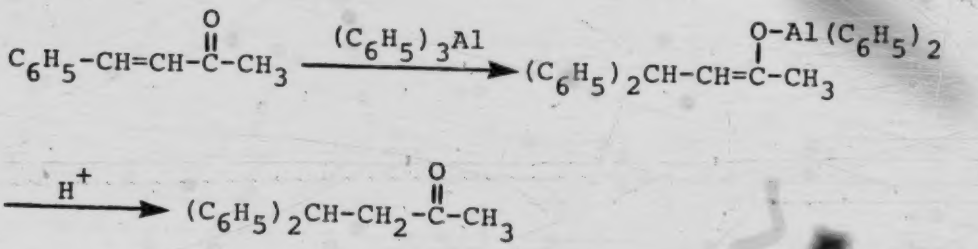


(10)

was observed by Hooz and Gunn that the intermediate enol borinate retains its regiointegrity as shown by specific deuterium incorporation after quenching with deuterium oxide.[48] Such enol borinates have been isolated and characterized by Pasto[49] and Köster[50-53] and their respective coworkers.

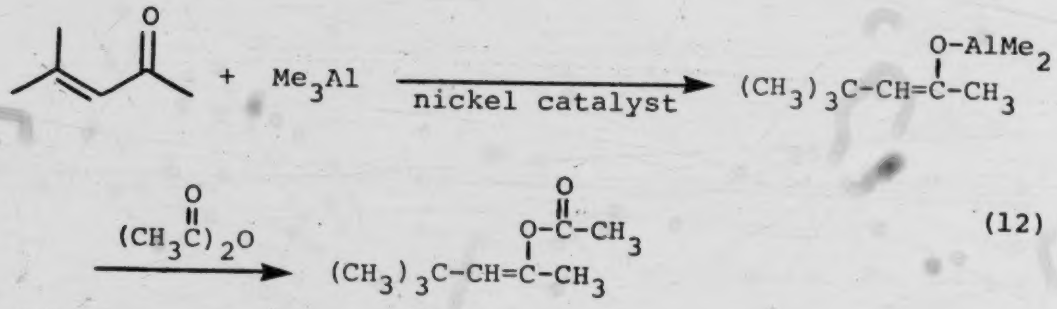
It was recently reported that alkenyl-[54] and alkynylboranes[55,56] undergo addition to enones in a 1,4-manner as well. This conjugate addition of organoboranes to enones offers a potentially valuable synthetic method because of the ready availability of organoboranes (e.g. hydroboration of olefins), and the stability of enol borinates towards proton transfer reactions.

2.f. Aluminum Enolates. These enolates have not been investigated as extensively as enol borinates, but a number of recent publications have appeared that show the potential value of these species. Wittig and coworkers[57] had earlier reported that triphenylaluminum adds exothermically to benzalacetone to give



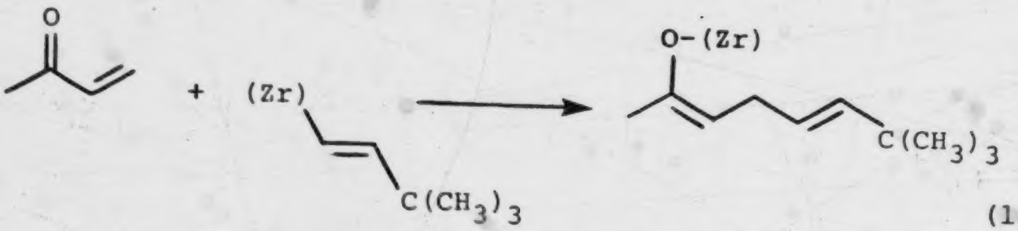
$$C_6H_5\text{-}CH{=}CH\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 \xrightarrow{(C_6H_5)_3Al} (C_6H_5)_2CH\text{-}CH{=}\overset{O\text{-}Al(C_6H_5)_2}{\overset{|}{C}}\text{-}CH_3 \xrightarrow{H^+} (C_6H_5)_2CH\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 \qquad (11)$$

4,4-diphenyl-2-butanone after hydrolysis, as shown in equation 11. Cyano-[58], alkynyl-[59-62], alkenyl-[62,63] and alkylaluminum[64-67] compounds have also been shown to react with enones to give the corresponding aluminum enolates, which are usually hydrolyzed to produce ketones, or reacted further *in situ*. These intermediates are also available from reaction of lithium[21] or zinc enolates[60] and dialkylaluminum chlorides. Aluminum enolates have been characterized by Mole and coworkers[65] who also showed that they are readily converted to enol acetates[65,67]. Thus, reaction of trimethylaluminum with mesityl oxide in the presence of a nickel catalyst produced a mixture of E- and Z-enol derivatives, which led to the formation of enol acetates upon treatment with acetic anhydride (eq. 12).



(12)

2.g. Organozirconium Enolates. These enol derivatives have only recently become of some interest in organic synthesis and their chemistry has yet to be explored in detail. Organozirconium compounds can be prepared by hydrozirconation of acetylenes and alkenes with $Cl(H)Zr(Cp)_2$. Alkenyl zirconiums undergo conjugate addition to enones[69,70] in the presence of nickel

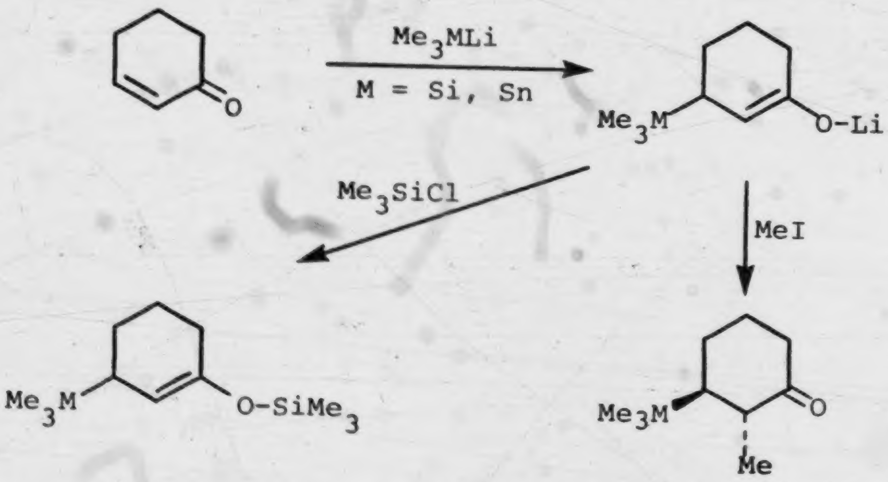

O
+
(Zr)
C(CH3)3
O-(Zr)
C(CH3)3

(13)

$(Zr) = (\eta^5\text{-}C_5H_5)_2Zr(Cl)\text{-}$

catalysts (eq. 13) to produce the corresponding zirconium "enolates", which have been isolated and characterized[69]. Such enol derivatives have found application in the synthesis of certain prostaglandins[70].

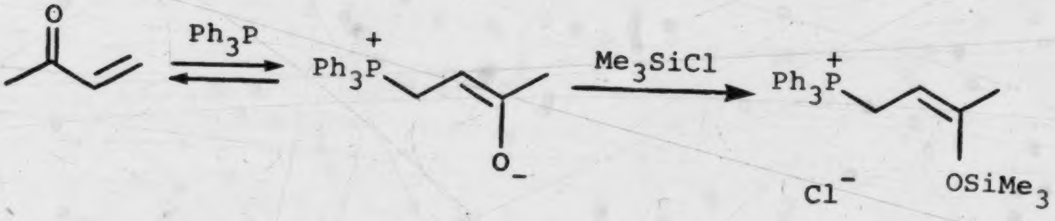
2.h. Addition of Trimethylsilyl- and Trimethylstannyllithium to Enones. Trimethylstannyllithium has been found to undergo a facile reaction with cyclohexenone to give a 1,2-addition product at -100°C, which equilibrates rapidly in THF or more slowly in ether to the 1,4-adduct[71,72]. The analogous trimethyl-


O
Me_3MLi
M = Si, Sn
Me_3M
O-Li
Me_3SiCl
MeI
Me_3M
$O\text{-}SiMe_3$
Me_3M
O
Me

(14)

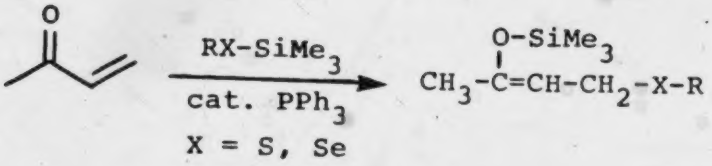
silyllithium, surprisingly, undergoes a direct conjugate addition leading to the corresponding enolate without the intermediacy of the 1,2-addition product[72,73]. The enolates derived from both reactions can be quenched with chlorotrimethylsilane to yield a regiospecific enol derivative or can be reacted with methyl iodide to give a single alkylation isomer (eq. 14).

2.i. Miscellaneous. An interesting observation has been made by Evans and coworkers[74], who reported that triphenylphosphine reacts with methyl vinyl ketone to form a phosphonium enolate, which is in equilibrium with the starting reactants (eq. 15). This enolate could be quenched, however, with chlorotrimethylsilane, resulting in the formation of a regioisomerically pure enol silyl ether.



(15)

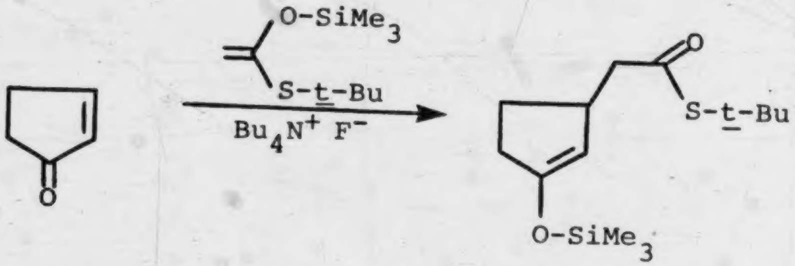
It was also shown that triphenylphosphine catalyzes the conjugate addition of phenyltrimethylsilylsulfides[74] and selenides[75] to enones as shown in equation 16. It has been suggested that phosphonium enol silyl ethers



(16)

(eq. 15) are intermediates in such reactions.

Certain enol silyl ethers have also been shown to undergo conjugate addition to enones[76,77] in the presence of fluoride and titanium catalysts to yield a new enol silyl ether[77]. For example, tetrabutylammonium fluoride catalyzes the 1,4-addition of the trimethylsilyl enol ether of S-t-butyl thioacetate to 2-cyclopentenone to give, regiospecifically, a new trimethylsilyl enol ether, which is a precursor of Jasmin ketolactone[77] (eq. 17).

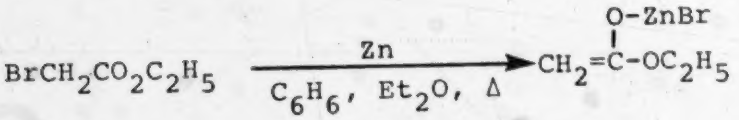


(17)

3. Enol(ate) Formation from α-Activated Carbonyl Compounds.

Enolates have been prepared via direct deprotonation of carbonyl compounds or via conjugate addition of certain nucleophiles to enones, but they can also be generated regiospecifically from ketones that have an activating group at the α-position (Scheme II). β-Keto esters are widely used for this purpose, but their extensive chemistry is beyond the scope of this introduction and has been reviewed elsewhere[2,5]. A number of interesting reactions have been developed during the last decade that utilize ketones with other α-substituents (e.g. α-bromo ketones, α-diazo ketones) and they are briefly discussed in this section.

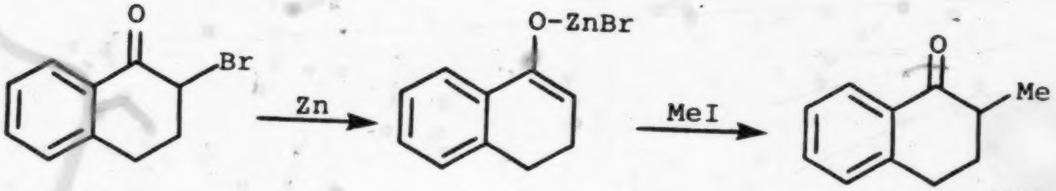
3.a. Reduction of α-Bromo Carbonyl Compounds. The reduction of α-bromo carbonyl compounds in inert solvents is a fairly general method to prepare metal enolates, and zinc has been found especially useful for this purpose. The Reformatsky reaction is among the oldest and best known procedures in this respect. Typically, an α-bromo ester is reduced with zinc to



$$BrCH_2CO_2C_2H_5 \xrightarrow[C_6H_6,\ Et_2O,\ \Delta]{Zn} CH_2{=}\overset{\overset{\displaystyle O\text{-}ZnBr}{|}}{C}\text{-}OC_2H_5 \qquad (18)$$

form a bromozinc enolate in the presence of an aldehyde or ketone[78,79], which reacts _in situ_ to afford β-hydroxy esters (eq. 18).

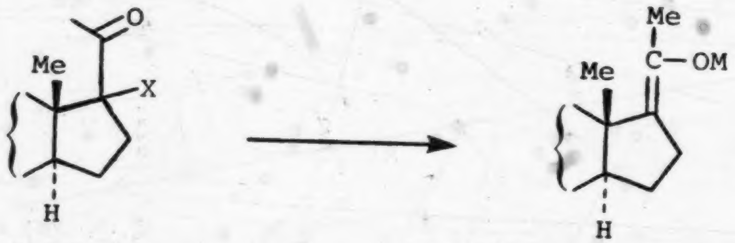
α-Bromo ketones have been similarly employed in the preparation of regiospecific enolates[80-85] _via_ reductive cleavage of the bromo substituent as illustrated in equation 19. This reaction appears to be limited to



(19)

carbonyl compounds that do not undergo self-condensation[80-82]. 2-Bromo-3-pentanone, for example, gave rise to a quantitative yield of a tetraalkylfuran upon treatment with either zinc[80] or magnesium[81]. This particular reaction must involve an aldol condensation reaction between the newly formed enolate and starting bromo ketone, thus severely limiting the scope of this approach.

Metal enolates can also by prepared from α-bromo-, α-acetoxy- and α-hydroxy ketones[83] under the conditions of a "dissolving metal reduction". Thus, a number of these derivatives were treated with metals (e.g. Na, Li, Ba and Ca) in liquid ammonia to produce regioisomerically pure enolates, which were subsequently employed in the alkylation of steroids (eq. 20). The

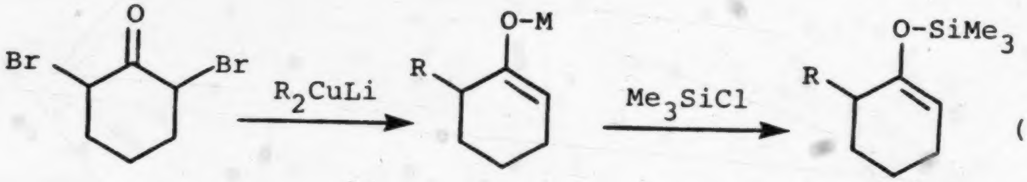


(20)

X = OH, Br, OAc

regiospecific preparation of enolates from α-acetoxy ketones was also exploited by A.J. Birch and coworkers in their synthesis of acoric acid[85].

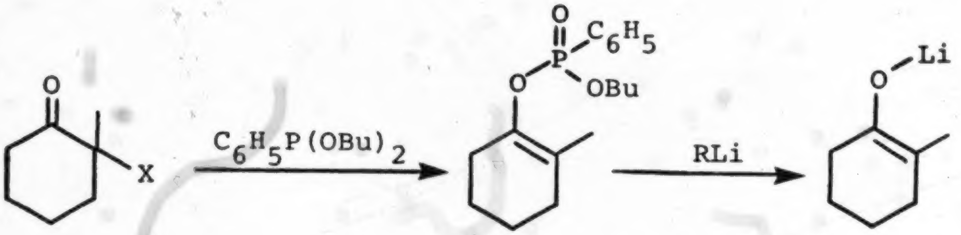
3.b. Addition of Cuprates. Organocopper "enolates" have been frequently generated by the conjugate addition of lithium dialkylcuprates to enones, but it is also possible to generate these enolates regiospecifically from the reaction of α-bromo ketones and cuprates[39,82,86,87]. Posner and Sterling[86] observed that 2-bromocyclododecanone reacts with lithium dimethylcuprate to give 2-deuteriocyclododecanone in excellent yield after D_2O work-up. Organocopper enolates can also be produced regiospecifically by reaction of lithium dialkylcuprates with α-dibromo ketones[87] or α,α'-dibromo ketones[39,86]. For example, the less highly substituted enolate of a 2-alkylcyclohexanone could be formed in this manner from 2,6-dibromocyclohexanone, which could be isolated as its trimethylsilyl enol ether (eq. 21). The reaction



(21)

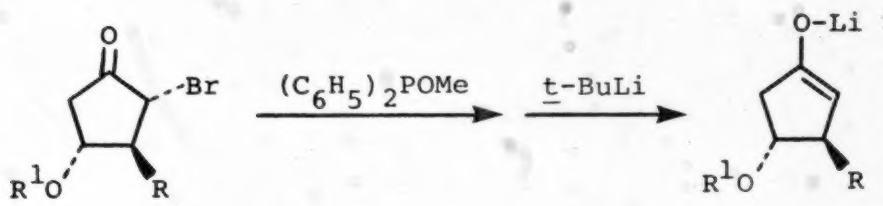
mechanism is believed to involve a cyclopropanone intermediate, which is followed by a substitutive ring-opening by the cuprate.

3.c. Phosphorylated Enol Derivatives. These compounds have been prepared by the reaction of α-halo ketones and alkyl diphenylphosphinites, dialkyl phenylphosphonites, and trialkyl phosphites[88]. This procedure prevents the formation of mixtures of regioisomeric enol derivatives, but they are usually not sufficiently reactive to undergo further alkylation. Borowitz and coworkers[89] showed that phosphorylated enols can be readily converted to their lithium enolates by the action of methyllithium as shown in equation 22.



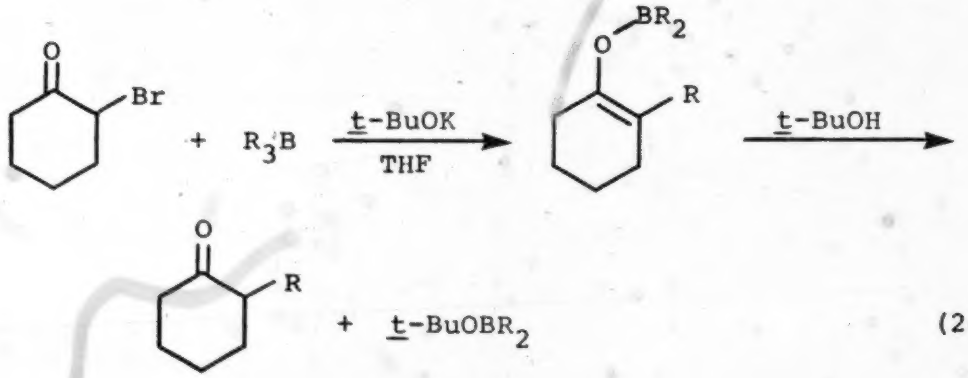
(22)

This method was elegantly applied by Stork and Isobe[90] in the synthesis of prostaglandins. In this case, a lithium enolate was generated from an appropriately substituted bromo cyclopentanone which in turn was readily available in two steps (via a bromohydrin reaction and a Jones' oxidation) from a cyclopentene derivative. Thus, the bromo ketone was reacted with methyl diphenylphosphinite to regiospecifically produce an enol phosphinate which subsequently was cleaved with tert-butyllithium as shown in equation 23.



(23)

3.d. Enol Borinates from α-Bromo Ketones. Trialkylboranes have been found to react with α-bromo carbonyl compounds in the presence of a suitable base resulting in the net displacement of the bromo substituent by an alkyl group[91,92]. For example, a 2-alkylcyclohexanone is produced under mild conditions and in good yields, when potassium tert-butoxide in tert-butyl alcohol is slowly added to a mixture of 2-bromocyclohexanone and a trialkylborane as shown in equation 24. The reaction appears to involve conversion



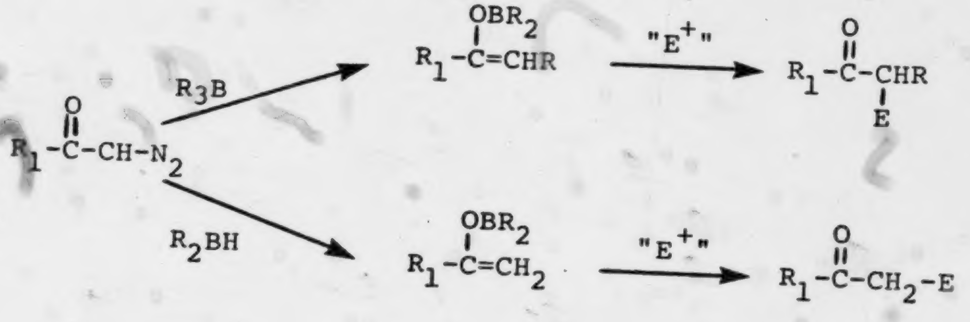
(24)

of the α-bromo ketone into the corresponding anion, formation of the "boron-ate" complex, and finally transfer of the alkyl group from boron to carbon which results in an enol borinate after tautomerization. This enol derivative is then hydrolyzed in situ by tert-butyl alcohol to give the alkylated cyclohexanone.

One must take into account, however, that the utilization of α-bromo ketones and similar derivatives for the generation of regiospecific enolates is only a partial solution since it is often difficult to synthesize such compounds in isomerically pure form. For example, the direct bromination of 2-pentanone leads to a mixture of 53% 3-bromo-2-pentanone and 32% 1-bromo-2-pentanone[92]. Although these derivatives have been occasionally prepared via indirect methods[90,93], they are often synthesized from enol derivatives themselves, such as enol acetates[94], enol silyl ethers[95] and enol borinates[96,97]. This in turn requires a regiospecific preparation or the often tedious separation of mixtures of such derivatives. Thus, the synthesis of isomerically pure α-bromo ketones is itself intimately associated with the general problems of enol(ate) chemistry.

3.e. Enol Borinates from α-Diazo Ketones.

Treatment of trialkylboranes with α-diazo carbonyls in THF leads smoothly under mild conditions to the regiospecific formation of enol borinates[96,98-105], which can be conveniently monitored by the gradual evolution of nitrogen (eq. 25). Trialkynylboranes[106] have also been reported to react in a similar manner to give ketones upon hydrolysis. The reaction is believed to involve the coordination of the borane to the α-carbon of the diazo carbonyl compound, followed by a migration of the alkyl group from boron to carbon with the concomitant displacement of molecular nitrogen, after which the dialkylboryl group tautomerizes to give the enol borinate.



$$R_1-\overset{O}{\overset{\|}{C}}-CH-N_2 \xrightarrow{R_3B} R_1-\overset{OBR_2}{\overset{|}{C}}=CHR \xrightarrow{"E^+"} R_1-\overset{O}{\overset{\|}{C}}-\underset{\underset{E}{|}}{CHR} \qquad (25)$$

$$R_1-\overset{O}{\overset{\|}{C}}-CH-N_2 \xrightarrow{R_2BH} R_1-\overset{OBR_2}{\overset{|}{C}}=CH_2 \xrightarrow{"E^+"} R_1-\overset{O}{\overset{\|}{C}}-CH_2-E \qquad (26)$$

Hydrogen was shown to have a greater migratory aptitude than alkyl groups in this reaction[107]. For example, dicyclohexylborane can be reacted with α-diazo ketones to give exclusively terminal enol borinates (eq. 26). Thus this synthetic method provides internal as well as terminal enol borinates in a regiospecific manner and appears to be very promising in view of the mild and essentially neutral reaction conditions. This type of reaction has also been reported to occur in cases where the nitrogen substituent of the α-diazo carbonyl compound is replaced by another leaving group (i.e. dimethylsulfonium)[49,108].

The present discussion of enol borinates (prepared from α-diazo ketones) is very brief, but a more complete survey will be given in part B of this chapter.

In conclusion, approaches to enolates are available via three general reaction types (as outlined in Scheme II):

(1) Proton abstraction from enolizable ketones is the most direct route, but this rarely leads to the regiospecific generation of enolates. It is possible, though, to influence the ratio of positional isomers by using the methods of kinetic or thermodynamically controlled deprotonation. "Masked carbonyls" can also be useful in the formation of certain regioisomers.

(2) "Dissolving metal reduction" of enones and conjugate addition of organometallic compounds results in site-specific enol(ate) formation. These methods have found wide application in the synthesis of steroids (cyclohexenone systems) and prostaglandins (cyclopentenone systems). Occasionally it has been used in the generation of site-specific

enolates in related compounds, e.g. cyclopropyl ketones.

(3) α-Substituted ketones lead to regiospecific enol(ate)s, in which the α-substituent is displaced. α-Bromo ketones have been frequently used to perform such a transformation, but it is often difficult to obtain these materials as regioisomerically pure substances. The use of α-diazo ketones appears to be especially valuable with respect to this limitation.

Part B. The Alkylation of Ketone Enolates[*].

The clean alkylation of enolates still remains a major obstacle in synthetic organic chemistry, despite the fact that regiospecifically generated enolates are now available via several routes. Usually, attempted alkylation is seriously complicated by di- and polyalkylation, loss of regiointegrity, aldolization and O-alkylation. Protecting and activating groups[2] are frequently used to force the alkylation to take place in one particular direction, but a discussion of such methods is beyond the scope of this introduction,

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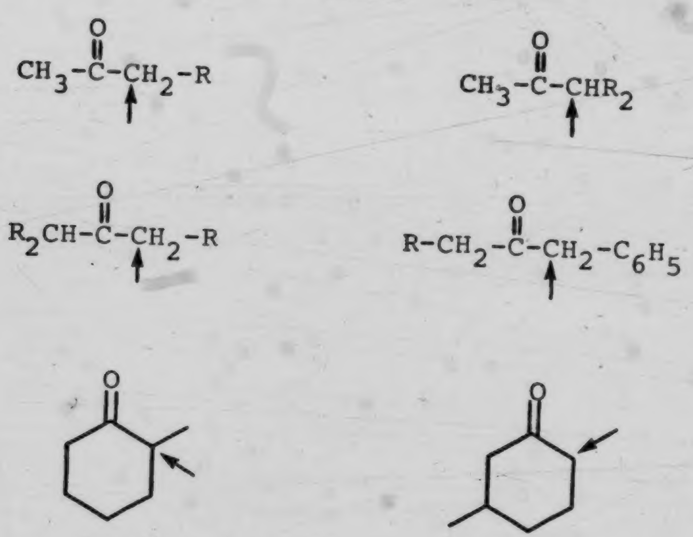
[*] Each section and subsection on alkylation corresponds to the respective (sub)sections in part A of this chapter concerning enol(ate) formation.

1a,b. A vast number of publications have appeared on the alkylation of ketone enolates (obtained from ketones via direct proton abstraction with strong bases), and only several selective examples of this process will be presented.

Ketones are alkylated in a preferred direction[1] when their enolates are treated with alkylating reagents under equilibrium conditions at the positions indicated in Scheme IV. For example, acyclic methyl alkyl ketones generally undergo alkylation at the more highly substituted position. In the case of cyclohexanone enolates, however, the preferred direction of alkylation under equilibrium conditions is usually determined by substituents at the α- and β- position, and this appears to be a result of a combination of steric and electronic factors.

Scheme IV



$CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{\uparrow}{CH_2}\text{-}R$

$CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{\uparrow}{CHR_2}$

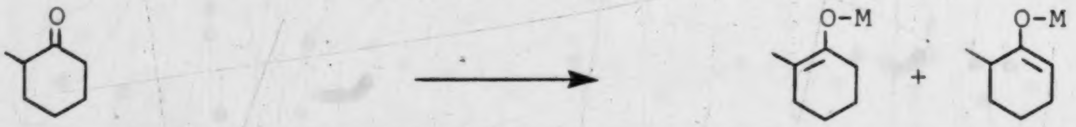
$R_2CH\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{\uparrow}{CH_2}\text{-}R$

$R\text{-}CH_2\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{\uparrow}{CH_2}\text{-}C_6H_5$

For example, the alkylation of 2-methylcyclohexanone was studied by Caine[109], and House and coworkers[6,110], and it can be clearly seen from the data of Table III, that the attempted methylation of this ketone leads to a complicated, difficultly separable mixture. The use of equilibrium conditions yields higher ratios of the α,α-dialkylcyclohexanone, while alkylation of the kinetically deprotonated 2-methylcyclohexanone favours the less substituted product. The ratio of regioisomeric enolates initially formed does not reflect the ratio of the corresponding α- and α' alkylated cyclohexanones, although regiointegrity is maintained to a certain extent in the case using a lithium cation. The recovery of starting material and presence of di- and polyalkylated products, moreover, indicate extensive proton transfer throughout the reaction.

It is nevertheless possible to alkylate certain ketones regiospecifically, depending on the equilibria and alkylation rates of the respective positional isomeric enolates. For example, the reaction of cholestan-3-one with potassium _tert_-butoxide and methyl iodide in boiling _tert_-butyl alcohol leads regiospecifically to 2α-methylcholestan-3-one and some 2,2-dimethylated product (eq. 27). Djerassi and coworkers also noted that methyl formate reacts in a similar way to give the 2-substituted β-dicarbonyl compound

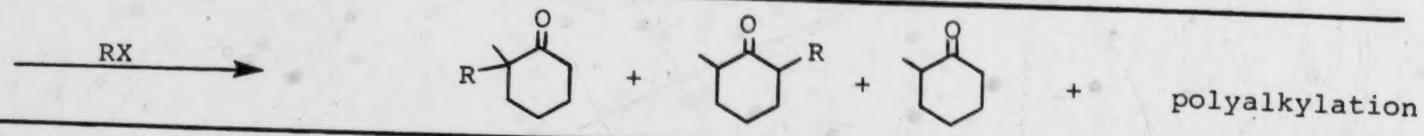
Table III. Product Distribution for the Reaction of 2-Methylcyclohexanone and Alkyl Halides in the Presence of Various Bases and Reaction Conditions[a]



entry	reaction conditions (base)	counter ion	enolate isomer, % Δ-1,2	enolate isomer, % Δ-1,6
1	equil. (Ph_3CK)	K^+	60	40
2	equil. (Ph_3CLi)	Li^+	--	--[b]
3	regiospecific[c]	Li^+	0	100
4	kinetic (Ph_3CLi)	Li^+	--	--[b]
5	kinetic (LDA)	Li^+	1	99

continued.....

Table III (continued)



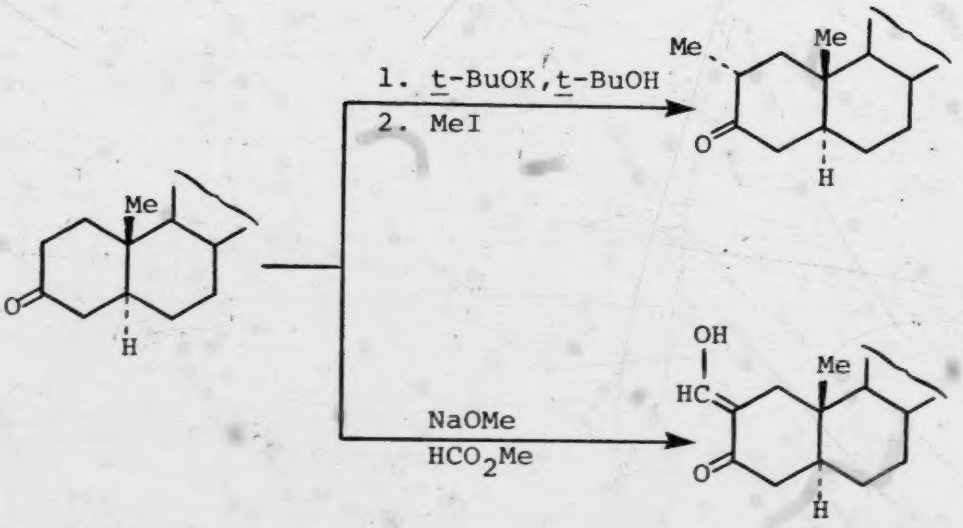
entry	RX	alkylation products 2R-	6R-	sm	polyalkylation
1	MeI	41	9	22	27
2	MeI	73	13	14	--
3	MeI	<10	72	16	12
4	MeI	<10	55	11	13
5	$C_6H_5CH_2Br$	3	59	--	--

[a] Reference, 6, 109 and 110.

[b] The ratio of positional isomers was not reported in this case.

[c] Prepared from 6-chloromercuri-2-methylcyclohexanone via reductive cleavage with lithium in liquid ammonia (ref. 109).

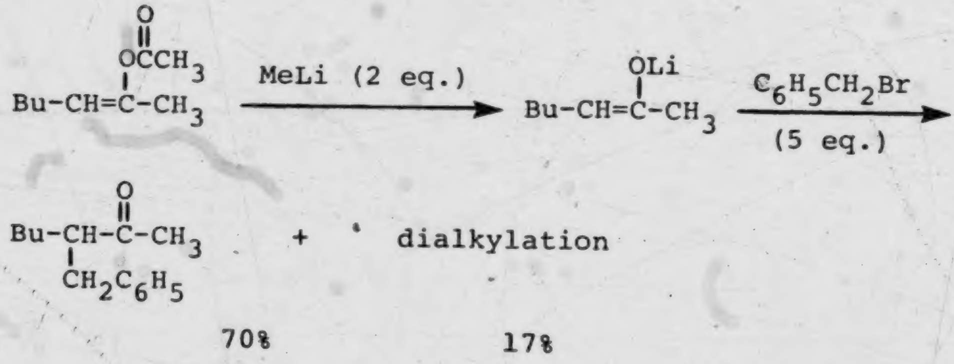
(eq. 28)[111].



(27)

(28)

It has been noted that acyclic enolates equilibrate faster than enolates of cyclic ketones, thereby enhancing the difficulties encountered in the alkylation of the former species[112]. House and coworkers[110] studied the alkylation of 2-heptanone and showed that even the alkylation of the more stable internal enolate gave rise to rather extensive proton transfer (eq. 29). The



$$\text{Bu-CH=}\overset{\overset{\overset{\text{O}}{\|}}{\text{OCCH}_3}}{\overset{|}{\text{C}}}\text{-CH}_3 \xrightarrow{\text{MeLi (2 eq.)}} \text{Bu-CH=}\overset{\text{OLi}}{\overset{|}{\text{C}}}\text{-CH}_3 \xrightarrow[\text{(5 eq.)}]{C_6H_5CH_2Br}$$

$$\text{Bu-}\underset{\text{CH}_2\text{C}_6\text{H}_5}{\underset{|}{\text{CH}}}\text{-}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-CH}_3 \quad + \quad \text{dialkylation} \qquad (29)$$

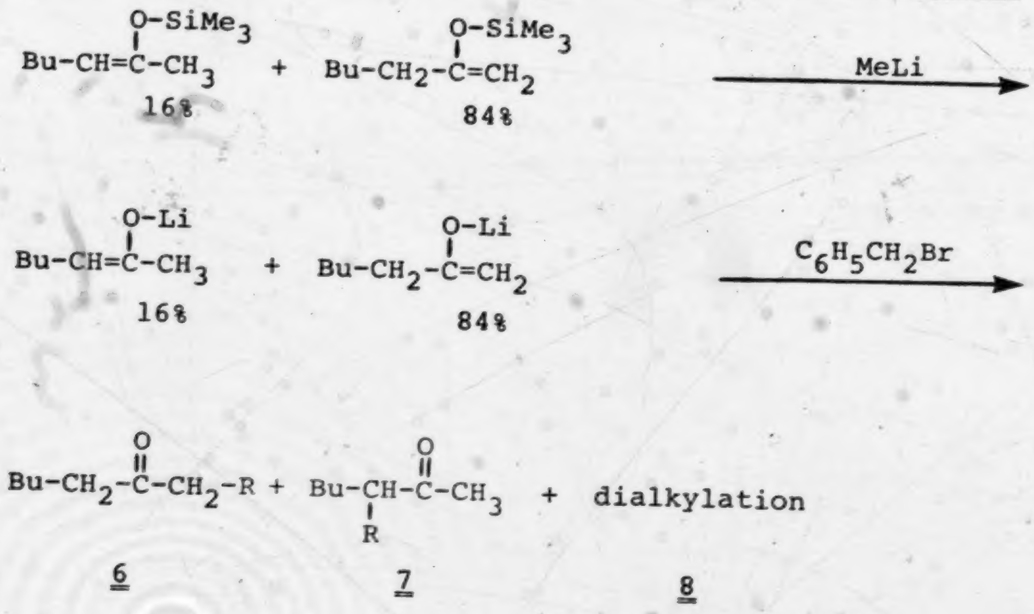
70% 17%

extent of dialkylation could be reduced by using the lithium enolate derived from the corresponding enol silyl ether. In this case tetramethylsilane is produced as by-product upon cleavage with methyllithium, and this is totally inert under the reaction conditions. In contrast, cleavage of the corresponding enol acetate with methyllithium gives rise to lithium tert-butoxide, and the latter can initiate further proton transfer, etc.

It was nevertheless shown that even in the absence of reactive by-products, acyclic and especially terminal lithium enolates undergo proton transfer faster than alkylation. Thus, the benzylation of the terminal enolate of 2-heptanone (prepared from the enol silyl ether, or, alternatively via direct kinetic deprotonation of 2-heptanone), produced complicated mixtures in which the desired product was only present in minor quantities, as shown in Table IV. These complex results are caused by a combination of an unfavourable position of the enolate equilibrium and an unfavourable ratio of alkylation rates of the isomeric enolates[110].

It is nevertheless possible to trap the kinetic enolate of methyl ketones when more reactive carbon electrophiles are employed. Thus Stork[113] and Gaudemar[114] have independently shown that terminal enolates could be regiospecifically alkylated with

Table IV. Product Distribution for the Reaction of Terminal Acyclic Lithium Enolates and Alkyl Halides[a,b]



$$\underset{16\%}{\mathrm{Bu{-}CH{=}\overset{O{-}SiMe_3}{C}{-}CH_3}} + \underset{84\%}{\mathrm{Bu{-}CH_2{-}\overset{O{-}SiMe_3}{C}{=}CH_2}} \xrightarrow{\mathrm{MeLi}}$$

$$\underset{16\%}{\mathrm{Bu{-}CH{=}\overset{O{-}Li}{C}{-}CH_3}} + \underset{84\%}{\mathrm{Bu{-}CH_2{-}\overset{O{-}Li}{C}{=}CH_2}} \xrightarrow{\mathrm{C_6H_5CH_2Br}}$$

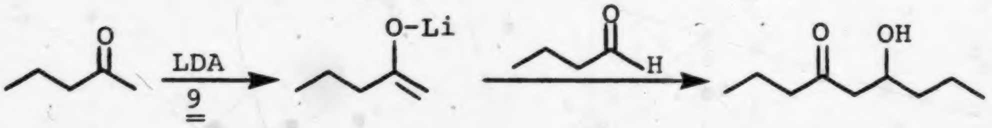
$$\underset{\underline{\underline{6}}}{\mathrm{Bu{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}CH_2{-}R}} + \underset{\underline{\underline{7}}}{\mathrm{Bu{-}\underset{R}{CH}{-}\overset{O}{\overset{\|}{C}}{-}CH_3}} + \underset{\underline{\underline{8}}}{\text{dialkylation}}$$

conc. (M)		time (min)	product (%)		
enolate	$C_6H_5CH_2Br$		6	7	8
0.2	1.0	1	27	19	5
0.2	0.2	45	15	33	24
0.2	0.2	120	1	41	12

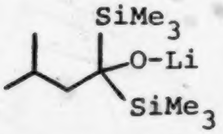
[a] Reference 110.

[b] These results are identical for the lithium enolates generated via kinetic deprotonation of 2-heptanone with LDA (ref. 110).

aldehydes (eq. 30). This reaction is carried out



(30)



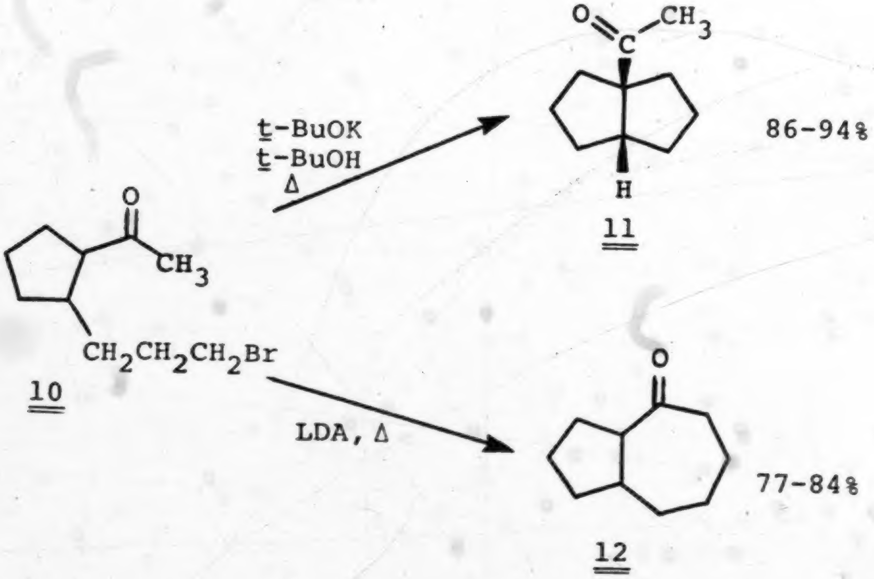
9

at -78°C, which appears to minimize proton transfer processes, although the overall process (deprotonation-alkylation) occurs with only ca. 85% regioselectivity.

It was later reported that "Mannich reagents" — e.g. dimethyl(methylene)ammonium trifluoroacetate — are also sufficiently reactive to undergo alkylation faster than proton transfer[115]. Kuwajima and coworkers[116] have shown that simple terminal lithium enolates could be formed and reacted regioselectively in the presence of aldehydes, using the highly hindered silyl alkoxide 9.

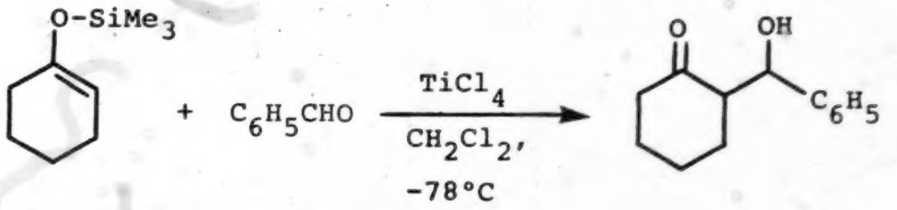
Certain terminal metal enolates, however, can be successfully intramolecularly alkylated with simple alkyl halides in cases wherein the product does not equilibrate with the unreacted starting enolate[117-119] as shown in Scheme V[118]. Thus the kinetic enolate of

Scheme V

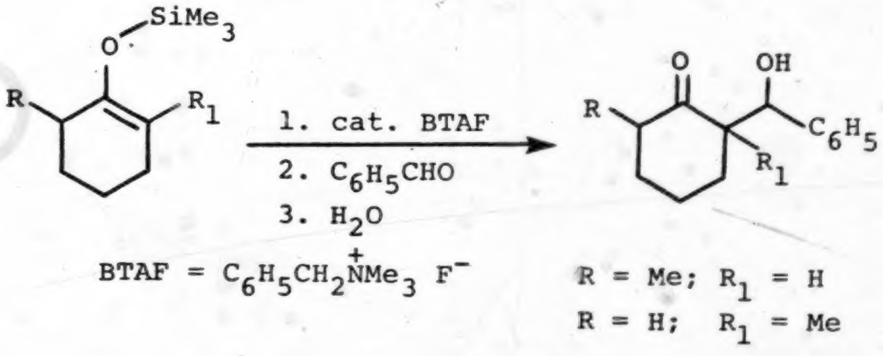


10 gave the seven-membered cyclic ketone 12 in very good yield along with only a trace of 11. In contrast, the thermodynamically more stable enolate, generated and alkylated under equilibrium conditions (t-BuOK in t-BuOH), gave exclusively the methyl ketone 11.

In recent years enol silyl ethers have become increasingly important in the construction of carbon skeletons[120]. Mukaiyama and coworkers[121] reported that such ethers react with aldehydes and ketones in the presence of $TiCl_4$ under mild conditions to give mixed aldol condensation products (eq. 31). Tertiary alkyl groups can be introduced in a similar way with tert-butyl chloride and $TiCl_4$ in reasonable yields[122].


O-SiMe$_3$
+ C_6H_5CHO
$TiCl_4$
CH_2Cl_2,
-78°C
O
OH
C_6H_5

(31)


SiMe$_3$
O
R
R_1
1. cat. BTAF
2. C_6H_5CHO
3. H_2O
O
OH
R
C_6H_5
R_1

(32)

BTAF = $C_6H_5CH_2\overset{+}{N}Me_3\ F^-$

R = Me; R_1 = H
R = H; R_1 = Me

Fluoride ions have also been reported to catalyze the reaction of enol silyl ethers with electrophiles (e.g. alkyl halides, aromatic aldehydes). These reactions occur with complete retention of regiointegrity as shown in equation 32[123,124]. For example, each positional isomeric enol silyl ether of 2-methylcyclohexanone leads to the corresponding regioisomerically pure β-hydroxy ketone upon reaction with benzaldehyde in the presence of a catalytic amount of benzyltrimethylammonium fluoride. The nature of the intermediate enolate species is not entirely clear and it has been postulated as being either a "naked enolate" or a pentavalent anionic silicon species.

"Mannich reagents", like dimethyl(methylene)-

ammonium iodide, are powerful electrophiles and they have been found to react directly with enol silyl ethers in the absence of a catalyst[125].

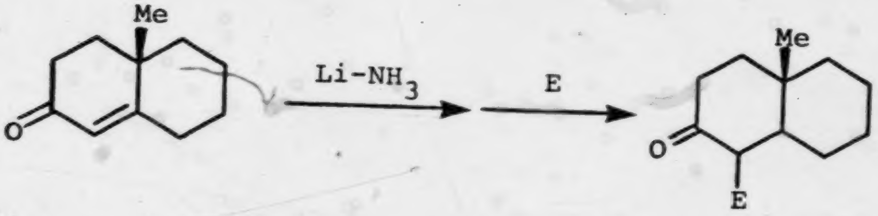
1.c. The alkylation of masked carbonyl compounds such as enamines[11] has been used to avoid some of the difficulties that are normally encountered (i.e. dialkylation and proton transfer reactions). Enamines of ketones and aldehydes react with electrophilic olefins (e.g. methyl vinyl ketones) to give high yields of monoalkylated product. On the other hand, alkylation with alkyl halides is generally restricted to the use of such strongly electrophilic reagents as methyl iodide, allyl bromides, and benzyl bromides[2,11]. Other alkyl halides have been found to produce N- rather than C-alkylated products. Enamines give rise, however, to preparatively useful yields of ß-diketones upon reaction with acyl halides[126].

The difficulties that are encountered during the alkylation of enamines - with regard to the ambident nature of these masked carbonyls - can be minimized when metallated imines are employed for this purpose[13]. This methodology has also been applied by Wittig and coworkers in the design of a mixed aldol condensation reaction[127].

The chemistry of N,N-dimethylhydrazones has recently been developed into a good synthetic method to alkylate methyl ketones regiospecifically[16] (eq. 3). A variety of electrophiles can be used in these reactions (e.g. primary and secondary alkyl halides, ketones, aldehydes, epoxides, and enones) to give good yields of the corresponding alkylated products.

2. The regiospecific generation and subsequent alkylation of enolates prepared from enones (especially cyclohexenone and cyclopentenone systems) has been studied by many research groups and some representative examples of this useful synthetic method will be discussed in the following section.

2.a. The "dissolving metal reduction" of octalones in the presence of lithium in liquid ammonia leads to an enolate that is not easily available *via* direct proton abstraction. It was shown that this enolate can be trapped regiospecifically with a variety of carbon electrophiles, e.g. alkyl halides[17,18], carbon dioxide[17], monomeric formaldehyde[22] and Michael acceptors[21] (eq. 33). It is important to exclude the

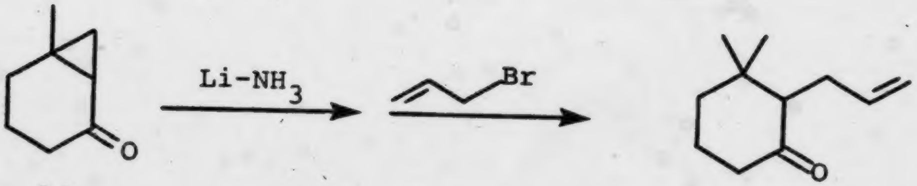


(33)

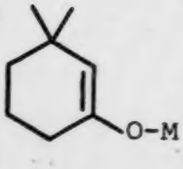
E: MeI, BuI, CO_2, CH_2O, α-silyl vinyl ketones.

presence of any proton donating sources, since loss of regiospecificity is otherwise observed[21]. However, complicated mixtures of alkylated ketones are obtained when this reduction-alkylation procedure is applied to simple acyclic enones[111].

2.b. Lithium enolates derived from reductive cleavage of cyclopropyl ketones have been alkylated regiospecifically with reactive alkyl halides[24,128] in good yields (eq. 6). For example, the β,β-disubstituted lithium enolate 15 (M = Li) formed during the "dissolving metal reduction" of the cyclopropyl ketone 13 underwent exclusive C-2 alkylation with allyl bromide in 70% yield (eq. 34).



13 14 (34)



15

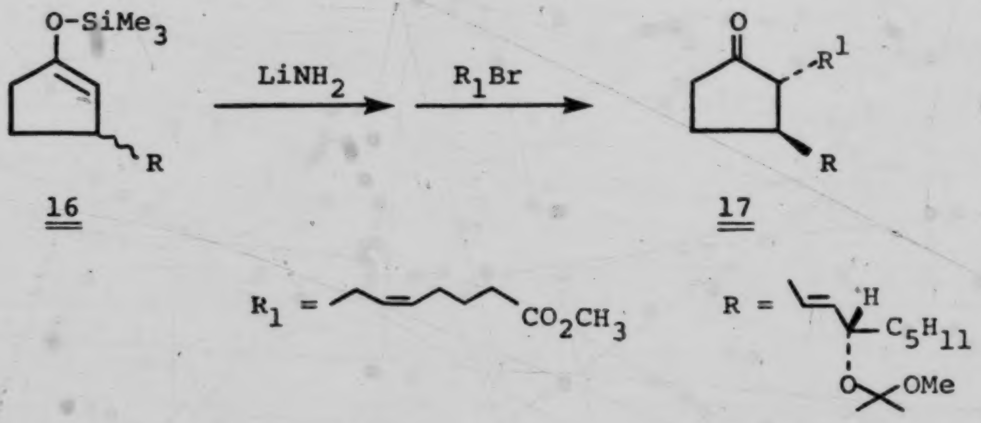
M = Li, MgI.

2.c. Magnesium enolates, prepared from the copper catalyzed conjugate addition reaction of Grignard reagents to enones, have been reported to undergo regiospecific alkylation with allyl bromide[26-31], aldehydes, and acyl chlorides[30] in the case of cyclohexenone derivatives. Thus, the iodomagnesium enolate 15 was prepared from methylmagnesium iodide and 3-methylcyclohex-2-enone in this manner, which was subsequently reacted with allyl bromide to produce ketone 14[30]. None of the regioisomeric ketone arising from C-6 alkylation could be detected, although this is the major product formed under equilibrium conditions[30].

Treatment of metal enolates with acetylating agents usually leads to enol acetates in high yields[6], but magnesium enolate 15 was found to give mainly the C-acetylated cyclohexanone upon reaction with acetyl chloride in ether. However, the reaction is solvent-dependent, since the enol acetate derived from 15 was the sole product when the reaction was carried out in DME.

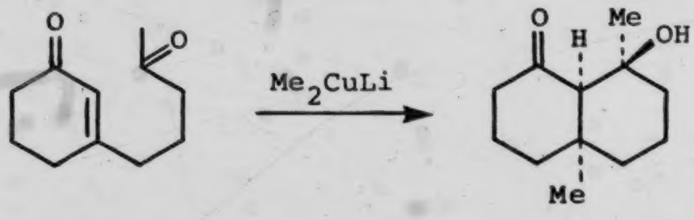
2.d. It has been suggested that "organocopper enolates", generated *via* conjugate addition of lithium dialkylcuprates to enones, would offer the possibility of eliminating the problems usually encountered in the alkylation of enolates, since "copper enolates" would presumably be highly covalent and therefore less likely to undergo proton transfer[33]. "Organocopper enolates" are rather unreactive however, requiring "activation" by HMPA, and are in fact operationally equivalent to lithium[8,26,37,128] and magnesium[26,28-30] enolates.

This method has nevertheless proven to be quite useful, especially in the field of prostaglandins[38,40-42]. The intermediate enolate species can be trapped with chlorotrimethylsilane to produce the corresponding enol silyl ethers, thus allowing purification and subsequent regiospecific conversion to a metal enolate[37,38]. The enol derivative 16 (eq. 8) could thus be successfully alkylated to give a mixture of 11-deoxy-PGE$_2$ 17 and 11-deoxy-8,12-epi-PGE$_2$ methyl esters (eq. 35). Clean monoalkylation with simple



(35)

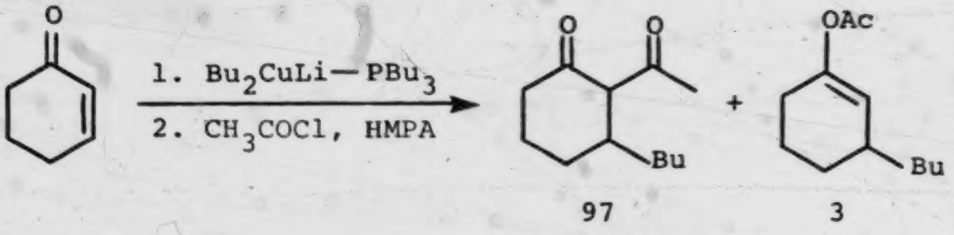
alkyl halides is not often observed in such systems however, due to rapid equilibration under the reaction conditions. Stork demonstrated that the more reactive electrophile, monomeric formaldehyde, acts as an effective trapping reagent for these enolates without competitive proton transfer reactions. This method has proven useful in the synthesis of prostaglandins[40]. Näf and coworkers[31] observed that lithium dimethylcuprate adds to enone 18 in the presence of a second carbonyl group to give aldol product 19 in both a regio- and stereospecific manner (eq. 36).



18 19

(36)

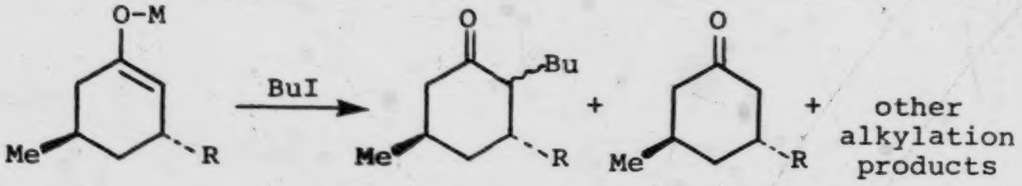
A Japanese reserach group reported that "organocopper enolates" — in the presence of phosphine ligands — undergo nearly exclusive C-acylation to yield β-diketones[41]. For example, cyclohexenone was treated with lithium dibutylcuprate and tributylphosphine, followed by acetyl chloride in HMPA to produce 2-acetyl-3-butylcyclohexanone along with a trace of the enol ester (eq. 37). This particular reaction was also applied to the synthesis of 7-oxoprostaglandins[41].


O
1. $Bu_2CuLi—PBu_3$
2. CH_3COCl, HMPA
O
O
Bu
97
+
OAc
Bu
3

(37)

Heathcock and Binkley have studied the influence of several metal counterions and the effect of HMPA on the alkylation of regiospecifically generated enolates (derived from cuprate addition to cyclohexenones)[37]. Table V summarizes their results, showing

Table V. Effect of Counterion and HMPA on the Alkylation of Enolates[a]

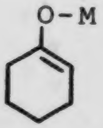

O-M
Me
R
BuI
O
Bu
Me
R
+
O
Me
R
+
other
alkylation
products

counterion M	solvent	product ratio (%) 2-Bu	2-H	by products
Li	THF-NH_3	96	4	0
Li	THF-HMPA	52	6	42
Na	THF-NH_3	35	34	31
K	THF-NH_2	49	8	43

[a] Reference 37.

that the addition of HMPA to a lithium enolate or changing to a more "ionic" enolate (i.e., Na or K counterion) has a detrimental effect and leads to by-products arising from α'-alkylation, dialkylation, and O-alkylation. The results obtained with the lithium enolate-HMPA system thus resemble more closely those from the more "ionic" potassium enolate system than the "covalent" lithium enolate system. Although it is tempting to correlate this effect with the extent of ionic character, the remarkable observation has been

Table VI. Effect of Counterion and HMPA on the Chemical Shift of the Vinylic Proton of Cyclohexanone Enolate[a,b]

		Chemical Shift (δ)	
		Additive	
compd.	M	none	HMPA[c]
	Me_3Si	4.83[d]	4.83
	MgBr	4.78[d]	4.62
	Li	4.16[d]	4.16
	K	~3.9[e]	~3.7

[a] Reference 8.

[b] Chemical shifts in ppm downfield from Me_4Si.

[c] Addition of 30-50% HMPA to the enolate solution.

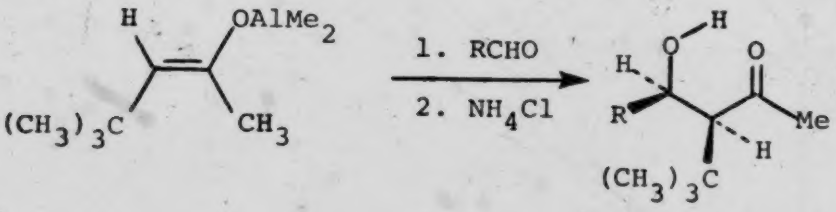
[d] In THF-d_8.

[e] In DME.

made by Stork and Hudrlik that addition of HMPA does not have any appreciable effect on the position of the vinyl proton absorption in the NMR spectrum[8] for various cyclohexanone enolates (M = Li, Mg and K) as shown in Table VI. The implication of the latter findings are that lithium enolates are not transformed into "free ions" by this (HMPA) dipolar aprotic solvent.

2.e. The alkylation reactions of enol borinates (prepared via the conjugate addition of organoboranes to enones) will be discussed in Section 3.d.

2.f. Mole and coworkers reported that aluminum enolates, derived from conjugate addition of trimethylaluminum to mesityl oxide in the presence of nickel catalysts, react rapidly with aldehydes at -20°C to give high yields of β-hydroxy ketones after hydrolysis. They observed that the reaction not only proceeded regiospecifically, but also with a high degree of stereoselectivity (eq. 38).



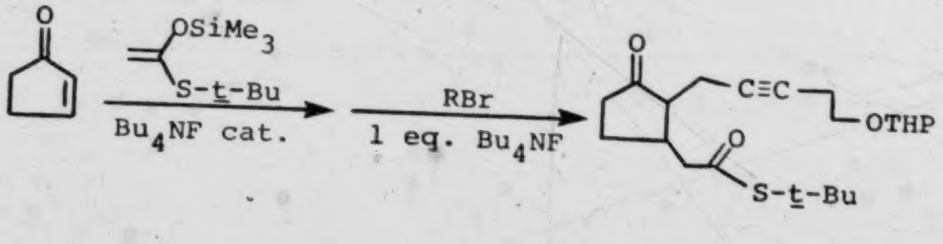
(38)

2.g. Zirconium enolates[69] have only recently been prepared and their chemistry has yet to be fully explored. Nevertheless, they fail to react satisfactorily with ordinary alkyl halides, but do react with more electrophilic species such as formaldehyde, and this has been employed in the synthesis of prostaglandin derivatives[70].

2.h. The lithium enolates generated from the conjugate addition of organotin[71] and silicon[73] compounds to cyclohexenone derivatives have been shown to undergo regiospecific methylation (eq. 14).

2.i. Although sulfur[74], phosphorous[74] and selenium[75] compounds have been reported to react with enones in a 1,4-manner as shown in equation 15 and 16, the resulting enol silyl ethers have not yet been shown to have synthetic utility.

An interesting example of the high regioselectivity of the fluoride catalyzed alkylation of enol silyl ethers[123,124] was recently reported by a Swiss research group[77] in the synthesis of (±)-Jasmin Ketolactone (eq. 39). A 1,4-addition reaction of a thioacetate



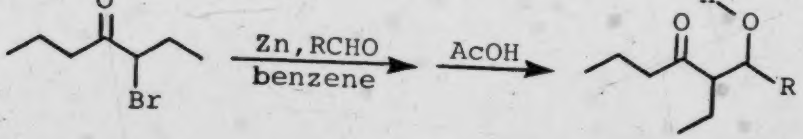
(39)

derivative to cyclopentenone led to the regiospecific formation of an enol silyl ether (eq. 17), which was subsequently reacted with one equivalent of tetrabutylammonium fluoride and a substituted propargyl bromide to produce a 2,3-disubstituted cyclopentanone (eq. 39). Further elaboration of this ketone gave rise to the desired natural product.

3. A final category of enolate alkylations is that of enol(ate)s derived from ketones that possess an activating group at the α-carbon, e.g. α-bromo ketones and α-diazo ketones.

3.a. Enolates which are formed in the reductive cleavage of α-bromo ketones are of limited utility when alkyl halides are used as electrophiles, and this reaction is therefore only applicable to ketones that do not undergo self-condensation[80,83].

The reaction is of value, however, when more reactive electrophiles (e.g. aldehydes) are employed and the entire operation conducted in situ. For example, addition of zinc to a mixture of an α-bromo ketone and an aldehyde led to the regiospecific formation of the corresponding β-hydroxy ketone[68,80,84] as shown in equation 40.



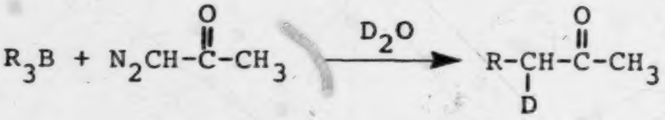
(40)

Another variation which appears to enhance the scope of the reaction is the simultaneous addition of the α-bromo ketone and aldehyde to a mixture of activated zinc and diethylaluminum chloride[68]. In this instance an intermediate aluminum enolate is presumably formed.

3.b. "Organocopper enolates" prepared from dialkylcuprates and α,α'-dibromo cyclohexanone (eq. 20) can be alkylated regiospecifically with rather reactive carbon electrophiles (e.g. MeI, Pr-CHO). With less reactive electrophiles, such as butyl iodide, for example, extensive proton transfer occurs, giving rise to isomeric mixtures of disubstituted cyclohexanones[39].

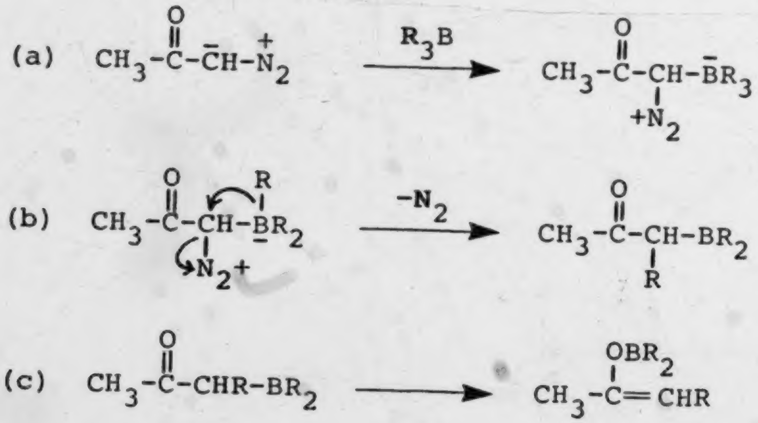
3.c. Phosphorylated enol derivatives are generally converted to the corresponding lithium enolates, since the former enol derivatives usually do not react with electrophiles directly. The alkylation behaviour of these species is thus equivalent to lithium enolates, which have already been discussed previously in this chapter.

3.d. The reaction of organoboranes and α-diazo ketones provides a mild method for the regiospecific construction of enol borinates[96-107]. These derivatives retain their regiointegrity, as shown by



$$R_3B + N_2CH-\overset{O}{\overset{\|}{C}}-CH_3 \xrightarrow{D_2O} R-\underset{D}{\underset{|}{CH}}-\overset{O}{\overset{\|}{C}}-CH_3 \qquad (41)$$

specific deuterolysis[48] (eq. 41) and bromination[96]. The mechanism of this reaction[49,98] is believed to involve an initial coordination of (a) the borane with the diazo ketone, (b) followed by a concerted migration of the alkyl group with displacement of nitrogen, (c) after which tautomerization of the dialkylboryl group takes place (eq. 42).

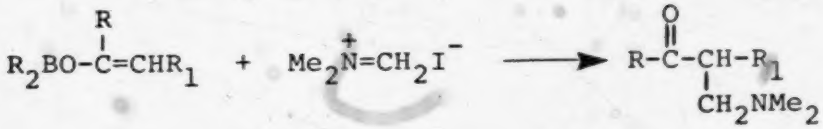


$$\text{(a)}\quad CH_3-\overset{O}{\overset{\|}{C}}-\bar{C}H-\overset{+}{N}_2 \xrightarrow{R_3B} CH_3-\overset{O}{\overset{\|}{C}}-\underset{+N_2}{\underset{|}{CH}}-\bar{B}R_3 \qquad (42)$$

$$\text{(b)}\quad CH_3-\overset{O}{\overset{\|}{C}}-\underset{N_2+}{\underset{|}{CH}}-\overset{R}{\overset{|}{\bar{B}}}R_2 \xrightarrow{-N_2} CH_3-\overset{O}{\overset{\|}{C}}-\underset{R}{\underset{|}{CH}}-BR_2$$

$$\text{(c)}\quad CH_3-\overset{O}{\overset{\|}{C}}-CHR-BR_2 \longrightarrow CH_3-\overset{OBR_2}{\overset{|}{C}}=CHR$$

Hooz and Bridson[96,105] studied the regiospecific alkylation of enol borinates, and observed that the "Mannich reagent", dimethyl(methylene)ammonium iodide, afforded excellent yields of α-dimetylamino ketones (eq. 43). Importantly, the positional isomer could



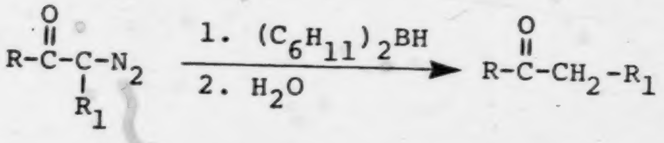
$$R_2BO\text{-}\overset{R}{\overset{|}{C}}\text{=}CHR_1 + Me_2\overset{+}{N}\text{=}CH_2I^- \longrightarrow R\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{CH_2NMe_2}{\underset{|}{CH}}\text{-}R_1 \qquad (43)$$

not be detected under the mild reaction conditions. Although enol borinates can be isolated by distillation[49-53], a separate isolation step is usually not necessary, since they can be unambiguously constructed by reaction of (a) trialkylboranes with α-diazo ketones (eq. 24), or (b) by conjugate addition of organoboranes to electrophilic olefins (eq. 10), and used *in situ*.

Neither of these routes, however, provides a method for the generation of a terminal enol borinate. Only the α-diazo ketone route could potentially lead to this type of enol borinate, if one could selectively transfer a hydrogen atom rather than an alkyl group. Benderly[107] subsequently showed that hydride migration is indeed the exclusive pathway in the reaction of α-diazo ketones and dicyclohexylborane or disiamylborane. The presumed mechanism of this reaction is analogous to the R_3B-α-diazo ketone reaction (eq. 42), in which one R group is replaced by a hydrogen.

The reaction was explored for a number of representative α-diazo ketones and the results are summarized in Table VII. 1-Diazo-2-heptanone and 1-diazo-5-

Table VII. Reaction of Several Representative α-Diazo Ketones with Dicyclohexylborane[a]



$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{R_1}{\underset{|}{C}}\text{-}N_2 \xrightarrow[2.\ H_2O]{1.\ (C_6H_{11})_2BH} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}R_1$$

α-diazo ketone		N_2 yield (%)	product yield (%)[b]
R	R_1		
C_5H_{11}-	H	98	93
$(CH_3)_2CHCH_2CH_2$-	H	90	85
$(CH_3)_2CH$-	H	75	70
-$(CH_2)_4$-		<20	--[c]

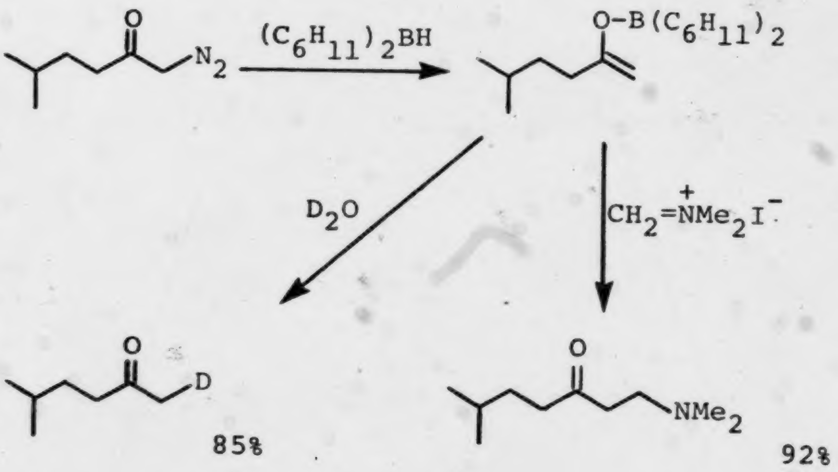
[a] Reference 107.

[b] Glc yields.

[c] The formation of the desired product, cyclohexanone, could not be detected.

methyl-2-hexanone led to excellent yields of the corresponding ketones (and thus of the precursor enol borinate), whereas the more sterically hindered 1-diazo-3-methyl-2-butanone led to a somewhat lower yield (70%). The reaction failed completely when 2-diazocyclohexanone was employed. The results of this investigation are thus a reflection of the steric requirements of the reaction, since the product yield progressively declines with the increasing steric bulk of the α-diazo ketone.

In summary, the terminal enol borinate derivatives prepared via this route retained their regiointegrity, as unambiguously shown by deuterolysis experiments and reaction with the "Mannich reagent" (eq. 44). (Thus,



(44)

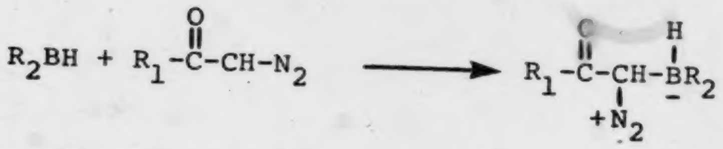
1-dimethylamino-6-methyl-3-heptanone could be prepared in this manner from the corresponding α-diazo ketone in 92% yield). This unambiguous site-specific construction of an enol derivative, and the experimental simplicity of the subsequent alkylation reaction, prompted a further exploration of the scope of this reaction in greater detail.

CHAPTER II

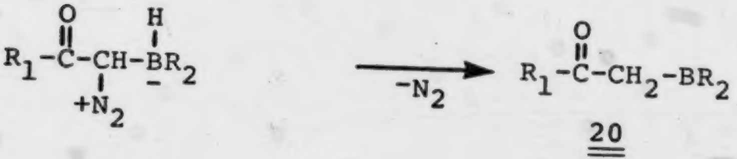
REGIOSPECIFIC ALDOL CONDENSATION REACTIONS

Part A. The Aldol Condensation of Terminal Enol Borinates of Methyl Alkyl Ketones.

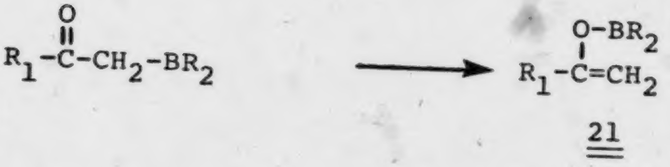
The reaction of dicyclohexylborane with α-diazo ketones is believed to lead to a terminal enol borinate, based on the similar chemical behaviour of this species and of (internal) enol borinates derived from the analogous trialkylborane reactions. The mechanism of this reaction is believed to proceed by initial borane coordination followed by hydride migration and tautomerization as illustrated in equation 45.



$$R_2BH + R_1-\overset{\overset{\displaystyle O}{\|}}{C}-CH-N_2 \longrightarrow R_1-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle +N_2}{|}}{CH}-\overset{\overset{\displaystyle H}{|}}{\underset{-}{B}}R_2 \qquad (45a)$$



$$R_1-\overset{\overset{\displaystyle O}{\|}}{C}-\underset{\underset{\displaystyle +N_2}{|}}{CH}-\overset{\overset{\displaystyle H}{|}}{\underset{-}{B}}R_2 \xrightarrow[-N_2]{} \underset{\underset{\displaystyle 20}{}}{R_1-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-BR_2} \qquad (45b)$$



$$R_1-\overset{\overset{\displaystyle O}{\|}}{C}-CH_2-BR_2 \longrightarrow \underset{\underset{\displaystyle 21}{}}{R_1-\overset{\overset{\displaystyle O-BR_2}{|}}{C}=CH_2} \qquad (45c)$$

α-Dialkylboryl ketones (e.g. 20) have never been isolated and appear to undergo fast tautomerization to enol borinates (21). Enol borinates have been purified by distillation[49-53] under inert (anhydrous and oxygen-free) conditions and are thermally stable, even at temperatures of 100°C and over. It was therefore expected that the isolation of the intermediate from the reaction of α-diazo ketones and dicyclohexylborane (eq. 45) would proceed without major complications.

Diazoacetone was chosen for study since the reaction product is easier to analyze by NMR spectroscopy (methyl group) and should have a lower boiling point than higher homologues. When the reaction was carried out at 5-7°C, followed by removal of THF and Kugelrohr distillation under reduced pressure, the NMR spectrum lacked the presence of the expected methyl and vinylic protons. Several attempts to isolate the intermediate in this manner failed, suggesting that the intermediate was not as stable as other internal enol borinates. Because distillation is the only practical purification method for these compounds (due to hydrolytic instability, etc.), the isolation of the pure intermediate was therefore abandoned.

The crude material was then processed by merely stripping off the THF and evacuating for several hours at room temperature. The NMR spectrum of the residue showed the presence of the methyl and vinylic protons, but only in minor concentrations. However, it was possible to obtain a satisfactory ^1H and ^{13}C NMR spectrum by simply repeating this procedure at slightly lower temperatures (0-5°C).

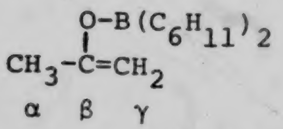
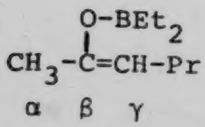
The C(α), C(β) and C(γ) absorptions in the CMR spectra are shown in Table VIII and are consistent with other enol derivatives (enol ethers, enol acetates)[129], and enol borinates[51] obtained from conjugate addition of triethylborane to methyl vinyl ketone. The proton absorptions are also quite similar to values published for other enol borinates[49,51] and enol acetates[6].

The terminal enol borinate (21) is unstable to storage since a sample kept at room temperature overnight in a sealed NMR tube showed the complete disappearance of the methyl and vinylic proton absorptions in the NMR spectrum. Nevertheless this does not restrict the synthetic utility of these terminal enol derivatives, since, as shown below, solutions of these intermediates can be conveniently reacted with various electrophiles - e.g. dimethyl(methylene)ammonium iodide[107] - in situ.

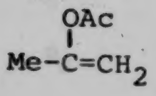
Since the structure of terminal enol borinates was thus adequately established, we explored their synthetic utility. It was of interest to determine whether alkylations, other than precedented Mannich reactions[107], would occur with retention of regiospecificity, thereby circumventing the problems which are ordinarily associated with alkylation of enolates.

Table VIII. ^{13}C and ^{1}H NMR Parameters of Terminal Enol Borinate 21 and Some Representative Enol Derivatives[a]

^{13}C NMR Chemical Shifts

compd.		C(α)	C(β)	C(γ)	cyclohexyl
 $\underset{\alpha}{CH_3}-\underset{\beta}{\overset{\overset{O-B(C_6H_{11})_2}{\vert}}{C}}=\underset{\gamma}{CH_2}$	(21)	22.1	156.5	95.5	~28
 $\underset{\alpha}{CH_3}-\underset{\beta}{\overset{\overset{O-BEt_2}{\vert}}{C}}=\underset{\gamma}{CH}-Pr$	Z	22.1	148.7	109.8[b]	
	E	17.1	149.0	111.0[b]	
$MeO-CH=CH_2$			153.1	85.5[c]	
$AcO-CH=CH_2$			141.7	96.4[c]	

^{1}H NMR Chemical Shifts

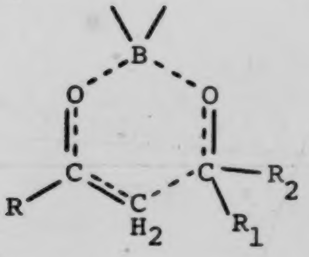
compd.	H(α)	H(γ)	cyclohexyl
21	1.9	4.4	2.1-1.1
 $Me-\overset{\overset{OAc}{\vert}}{C}=CH_2$	1.8	4.5-4.7[d]	

---

[a] Chemical shifts in ppm relative to $(CH_3)_4Si$.

[b] Reference 51. [c] Reference 129. [d] Reference 6.

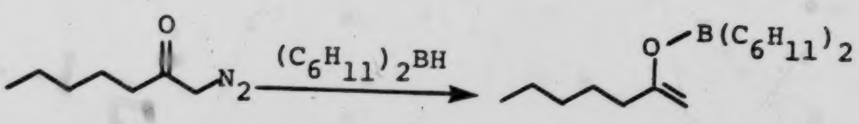
It appeared that reaction of terminal enol borinates with carbonyl compounds would be a potential route to isomerically pure aldol condensation products, especially because such a transformation could conceivably take place via a favourable six-membered transition state (structure 22), after the enol borinate



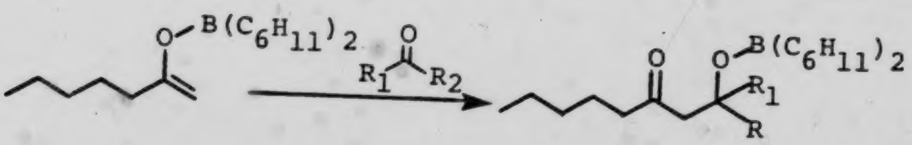
22

and carbonyl compound formed the initial Lewis acid-base complex.

Thus, the terminal enol borinate obtained from 1-diazo-2-heptanone and dicyclohexylborane was reacted in situ with several carbonyl compounds (acetone, acetaldehyde, and benzaldehyde). The resulting mixture was subsequently oxidized with hydrogen peroxide (30%) in aqueous sodium acetate to give a mixture of β-hydroxy ketone 24 and cyclohexanol (the latter is formed by the oxidative work-up procedure as illustrated in equation 46c). Isolation of the aldol product proved to be rather difficult, since column chromatography (silica gel or Florisil) led to extensive β-

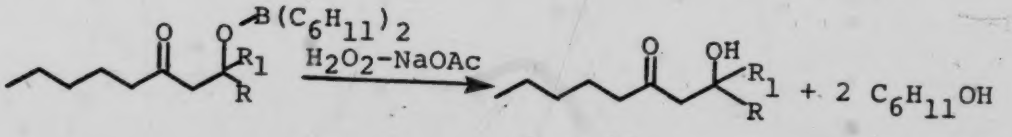


(46a)



23

(46b)



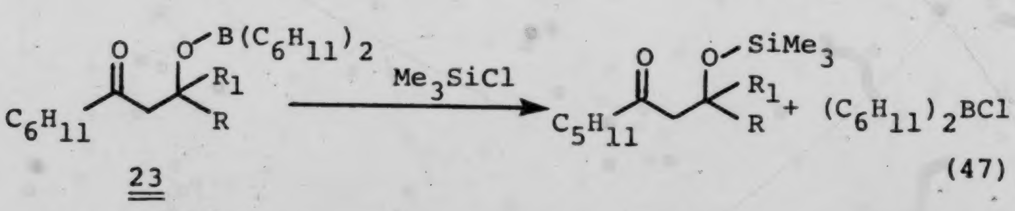
24

(46c)

elimination yielding α,β-unsaturated ketones. Simple distillation under reduced pressure did not separate the two main components since their boiling points were too close, while distillation using a spinning band apparatus again gave rise to the formation of α,β-unsaturated ketones.

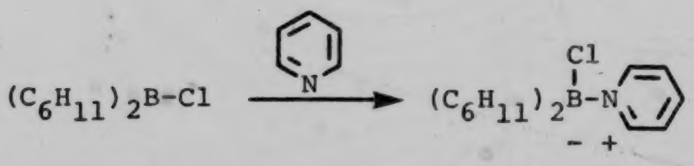
The crude mixture was then oxidized with hydrogen peroxide, followed by treatment with chlorotrimethylsilane and pyridine, in an attempt to trap the aldol as its trimethylsilyl ether derivative. The β-trimethylsilyloxy ketone was more resistant towards β-elimination but its isolation from the cyclohexanol derivative proved to be very difficult.

The dicyclohexyl borinate 23 was then reacted directly with chlorotrimethylsilane in order to circumvent the formation of cyclohexanol (eq. 47).



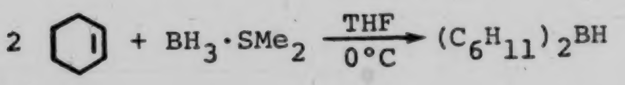
The resulting by-product, presumably chlorodicyclohexylborane, was not air-stable and again led to substantial amounts of cyclohexanol during attempted isolation.

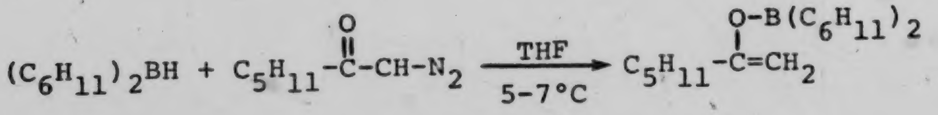
The addition of amines to the boron-containing by-product was next explored since many boranes are known to form stable B-N "ate" complexes[130,131], which could possibly facilitate the isolation of the desired product. For example, borane[132] and trimethylborane[133] react exothermically with pyridine to give the corresponding "ate" complex, and triethanolamineborate[134] has been shown to possess a strong transannular additive bond.



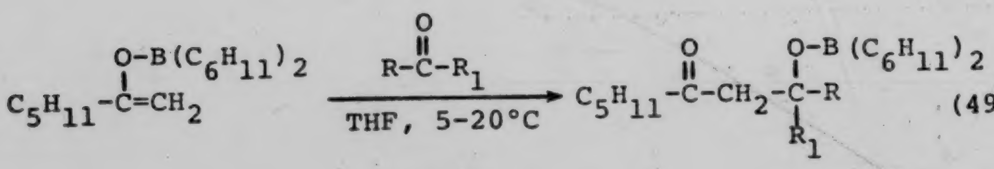
Thus, the crude aldol condensation product was treated with chlorotrimethylsilane (eq. 47), followed by addition of pyridine (eq. 48). A precipitate soon appeared (presumably a borane-amine "ate" complex of chlorodicyclohexylborane and pyridine), but it proved impracticable to remove the boron-containing by-product completely, despite repeated precipitation in pentane. It was furthermore difficult to prevent the formation of small amounts of cyclohexanol (air oxidation?).

Although these results fell short of developing a convenient isolation procedure, it was also apparent that this approach was worth pursuing further. Toward this end, the formation of a stable borane-amine complex with a "covalent" boron-nitrogen bond was subsequently investigated. This appeared a very attractive possibility since several silylating reagents that possess a silicon-nitrogen bond are available.

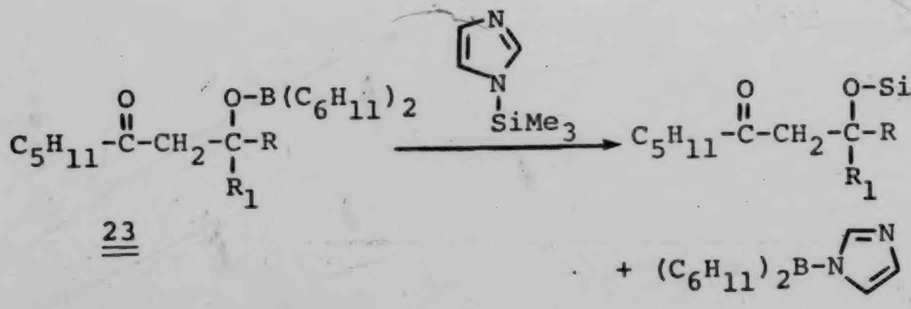

(49a)



$$(C_6H_{11})_2BH + C_5H_{11}\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH\text{-}N_2 \xrightarrow[5\text{-}7°C]{THF} C_5H_{11}\text{-}\overset{O\text{-}B(C_6H_{11})_2}{\overset{|}{C}}{=}CH_2 \qquad (49b)$$



$$C_5H_{11}\text{-}\overset{O\text{-}B(C_6H_{11})_2}{\overset{|}{C}}{=}CH_2 \xrightarrow[THF,\ 5\text{-}20°C]{R\text{-}\overset{O}{\overset{\|}{C}}\text{-}R_1} C_5H_{11}\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_2\text{-}\underset{R_1}{\underset{|}{\overset{O\text{-}B(C_6H_{11})_2}{\overset{|}{C}}}}\text{-}R \qquad (49c)$$


23

(49d)

Hence the exchange of the dicyclohexylboryl by a trimethylsilyl group was attempted by treating a solution of the intermediate dicyclohexylborinate 23 with N-(trimethylsilyl)imidazole as shown in equation 49d. The reaction occurred under mild conditions and appeared to be virtually instantaneous at room temperature. After concentration, simple distillation afforded the protected β-hydroxy ketone in good yields. The boron-imidazole by-product was a non-distillable waxy solid, which softened at temperatures above 200°C. This material proved to be inert to the aldol condensation product even at temperatures of ca. 150°C, since the formation of α,β-unsaturated ketones was usually not observed under these conditions.

Having established a convenient work-up and isolation procedure, it was then shown that the entire reaction sequence could be conducted in a single reaction vessel. For example, treatment of a suspension of dicyclohexylborane in THF (prepared in situ from cyclohexene and borane-methyl sulfide complex) with 1-diazo-2-heptanone, followed sequentially by one equivalent of 2-butanone (after the evolution of nitrogen had ceased) and N-TSIM, afforded after distillation, a 72% isolated yield of 3-methyl-3-trimethylsilyloxy-5-undecanone (eq. 49). Other examples are illustrated in Table IX.

Table IX. Formation of Aldol Condensation Products by Reaction of Terminal Enol Borinates with Aldehydes and Ketones (eq. 49)

entry	R	R_1	N_2, %	yield[a], %
1	CH_3	H	90	70 (90)
2	CH_3	CH_3	89	74
3	CH_3	C_2H_5	94	72
4	C_6H_{11}	H	90	40 (60)
5	C_6H_5	H	90	70[b]
6	H	H	93	33

[a] GLC yields in parentheses.

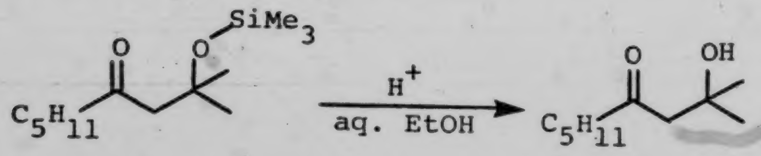
[b] Isolated as 1-phenyl-1-octen-2-one.

This method allows the synthesis of a number of interesting aldol condensation products under mild and essentially neutral reaction conditions. For example, the terminal enol borinate reacts smoothly with acetaldehyde to give a 90% yield of 2-trimethylsilyloxy-4-nonanone (Table IX, entry 1), although acetaldehyde is known to undergo a very facile self-condensation in the presence of catalytic amounts of acid or base[135]. Other aldehydes give also serviceable yields of regioisomerically pure derivatives of β-hydroxy ketones (Table IX, entries 4 and 5).

The use of formaldehyde as an electrophile led to a rather low yield of the corresponding aldol condensation product. Although formaldehyde was introduced into the reaction mixture as its monomer[22] (by pyrolysis of dry paraformaldehyde), the rate of repolymerization was apparently competitive with the aldol condensation. Several attempts to suppress this side reaction by using lower temperatures did not lead to any improvement.

Treatment of these terminal enol borinates with ketones also produced good yields of the corresponding β-hydroxy ketone derivatives (Table IX, entries 2 and 3). It is possible in this manner to formally construct one single structural isomer from two very similar ketones, as exemplified in the synthesis of 3-methyl-3-trimethylsilyloxy-5-decanone (Table IX, entry 3), from the terminal enol borinate of 2-heptanone and 2-butanone.

The free β-hydroxy ketone could be quantitatively obtained by hydrolyzing the β-trimethylsilyloxy ketone, as illustrated in equation 50. Thus, 2-methyl-2-tri-



(50)

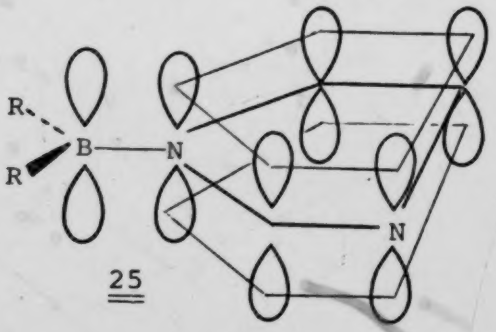
methylsilyloxy-4-nonanone was dissolved in aqueous ethanol, a drop of aqueous HCl was added, and the mixture was briefly warmed, after which the corresponding ketone could be easily isolated by distillation.

The use of this particular protecting group thus proved to have a number of important advantages. It prevented β-elimination during the isolation and purification procedure and, importantly, it permitted the separation of the dicyclohexylboryl moiety from the desired product.

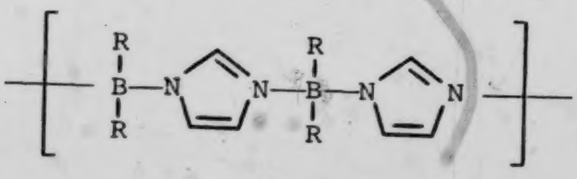
The favourable "inert" properties of the "amine-borane" by-product (air-stable, non-volatile) were also an added bonus.

However, isolation of the by-product, (1-imidazolyl)-dicyclohexylborane, as a pure substance for purposes of characterization, proved to be very difficult. Attempts to recrystallize this material failed repeatedly and yielded waxy solids, but a white precipitate could ultimately be obtained upon careful addition of acetone to a solution in chloroform. This material had no distinct melting point but softened above 220°C. Two structural possibilities seemed reasonable - either a monomer (25), or an oligomer (26). In 25, the boron-nitrogen bond could conceivably be strengthened *via* pπ-pπ interaction, in which delocalization of the aromatic ring extends through the electron deficient boron orbital.

Alternatively, stabilization could be provided by organoborane-Lewis base adduct formation, as in the "polymeric" chain-like structure 26.



25



26

The ^1H NMR spectrum ($CDCl_3$) exhibited two broad singlets at δ 7.5 and δ 6.8 (imidazolyl protons, relative intensities: 1.0 and 2.0) and a broad hydrocarbon envelope for the cyclohexyl groups at δ 0.0-3.0 (relative intensity: 22). The mass spectrum, however, revealed the "polymeric" nature of this compound. The highest boron-containing set of peaks corresponds to a trimeric species (M_3-R, M_3-Im). Further fragmentation yields dimeric and monomeric species and corresponding fragments arising from the loss of an alkyl or imidazolyl group, respectively (Table X). Ebullioscopic measurements gave molecular weights between 500 and 3000

(calcd. M.W. is 244)

Table X. Mass Spectral Data[a] for (1-Imidazolyl) dialkylboranes (26)

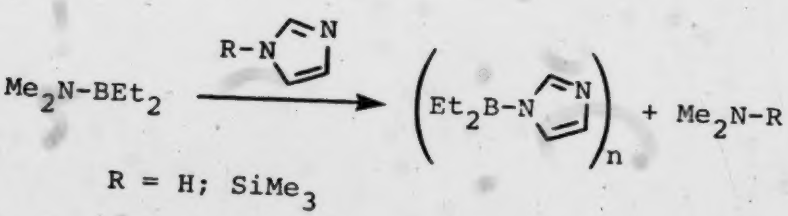
fragments, m/e	intensity[b], %	
	R = cyclohexyl	R = ethyl[c]
M_4-R	-	7.8
M_3-R	3.1	10.3
M_3-Im	0.8	28.9
M_2-R	0.3	17.7
M_2-Im	2.4	100
M	3.3	26.3
M-R	100	89.0
R	89.1	-

[a] At 70 eV, inlet temperature at 250-280°C.

[b] Relative to base peak.

[c] Reference 137.

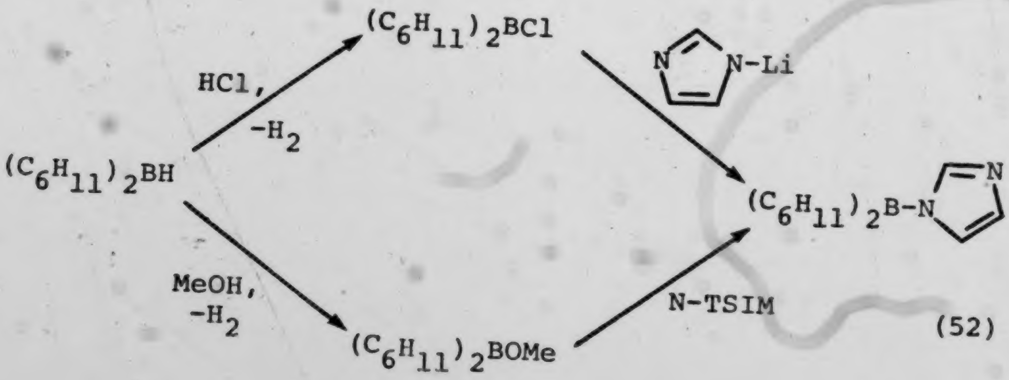
Based on these spectroscopic results a chain-like "polymeric" structure 26 is indicated, in which the nitrogen at the 3-position of the imidazolyl ring acts as a Lewis base to a second borane molecule. These results are analogous to (1-imidazolyl) diethylborane[136] that very recently has been synthesized and characterized by Niedenzu and coworkers[137]. This compound was prepared by reaction of (dimethylamino)diethylborane with either imidazole or N-TSIM (eq. 51).


Me2N-BEt2
R-N
N
Et2B-N
N
n
+ Me2N-R
R = H; SiMe3

(51)

These workers found that viscosity measurements gave molecular weights ranging from 6,000 to 12,000 and their spectroscopic data (infrared and MS) were quite similar to the dicyclohexyl derivative found in our work (Table X).

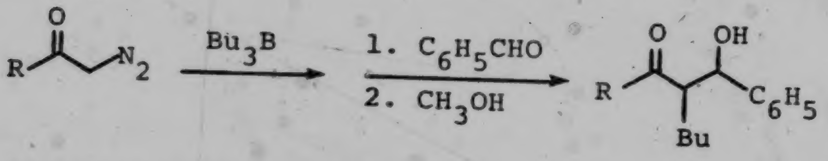
Independent synthesis of (1-imidazolyl)dicyclohexylborane was also accomplished via the different routes illustrated in equation 52. Thus, dicyclo-


(C6H11)2BCl
HCl,
-H2
N
N-Li
(C6H11)2BH
(C6H11)2B-N
N
MeOH,
-H2
N-TSIM
(C6H11)2BOMe

(52)

hexylborane could be reacted with hydrogen chloride and 1-lithio imidazole to give the desired compound. Alternatively, it could be prepared by successive treatment of dicyclohexylborane with methanol and N-(trimethylsilyl)imidazole.

It has also been shown by Mukaiyama and coworkers[138,139] that certain enol borinates undergo aldol condensation reactions as outlined in equation 53.



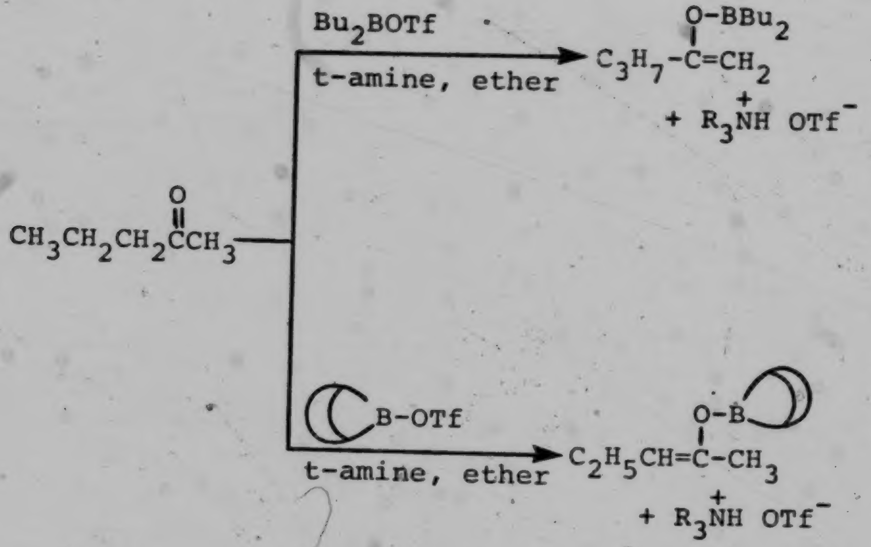
(53)

R = C_6H_5, EtO-.

27

For example, the enol borinate of pentyl phenyl ketone (from tributylborane and diazoacetophenone) reacted with benzaldehyde to give the corresponding β-hydroxy ketone 27 after methanolysis. The question of proton transfer and regiospecificity, however, obviously does not arise in the case of these particular carbonyl compounds.

Near the completion of this study, Mukaiyama and coworkers reported that terminal enol borinates could be obtained in high regioselectivity by the reaction of methyl ketones and dibutyl boron triflate in the presence of sterically hindered amines, e.g. diisopropylethylamine and 2,6-lutidine (eq. 54)[140]. These terminal enol borinates were reacted in situ with aldehydes to give β-hydroxy ketones in good yields upon hydrolysis.


Bu2BOTf
t-amine, ether
C3H7-C=CH2
O-BBu2
+ R3NH OTf−
CH3CH2CH2CCH3
O
B-OTf
t-amine, ether
C2H5CH=C-CH3
O-B
+ R3NH OTf−

(54)

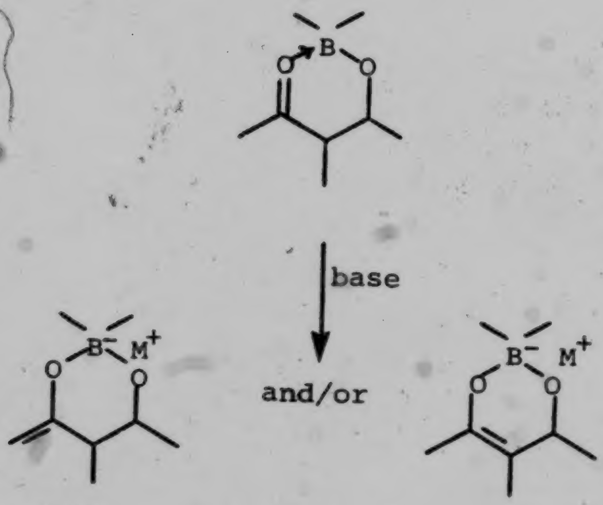
(55)

It was also reported that the use of 9-trifluoromethylsulfonyl-9-BBN leads regioselectively to the internal enol borinate[141] as illustrated in equation 55. As a result, several complementary methods now become available for aldol construction via enol borinates.

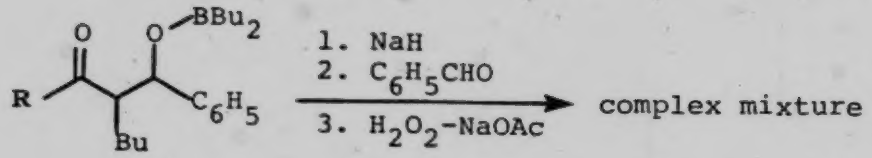
Part B. Mixed "Di"-Aldol Condensation Reactions.

The possible formation of mixed "di"-aldol condensation products was next examined. Since the reaction of enol borinates and aldehydes leads regiospecifically to β-dialkylboryloxy ketones, it was of interest to examine the deprotonation of these intermediates. In principle, proton abstraction could lead to either a cyclic "exo" **28** or "endo" **29** enoxy borinate complex as illustrated in Scheme VI. It was anticipated that such "enolates" should be sufficiently reactive to undergo a second aldol condensation reaction, leading to either α,α'- or α,α-"di"-aldol condensation products.

Scheme VI



Diazoacetone was reacted with tributylborane and benzaldehyde to give the aldol product 30, which was then treated with sodium hydride. A gas evolved in nearly quantitative yield, but subsequent reaction with benzaldehyde led to complicated mixtures that could not be identified (eq. 56). The use of diazoacetophenone in an attempt to avoid potential complications (with regard to regiochemistry) also yielded complex mixtures. This approach was therefore abandoned.



30

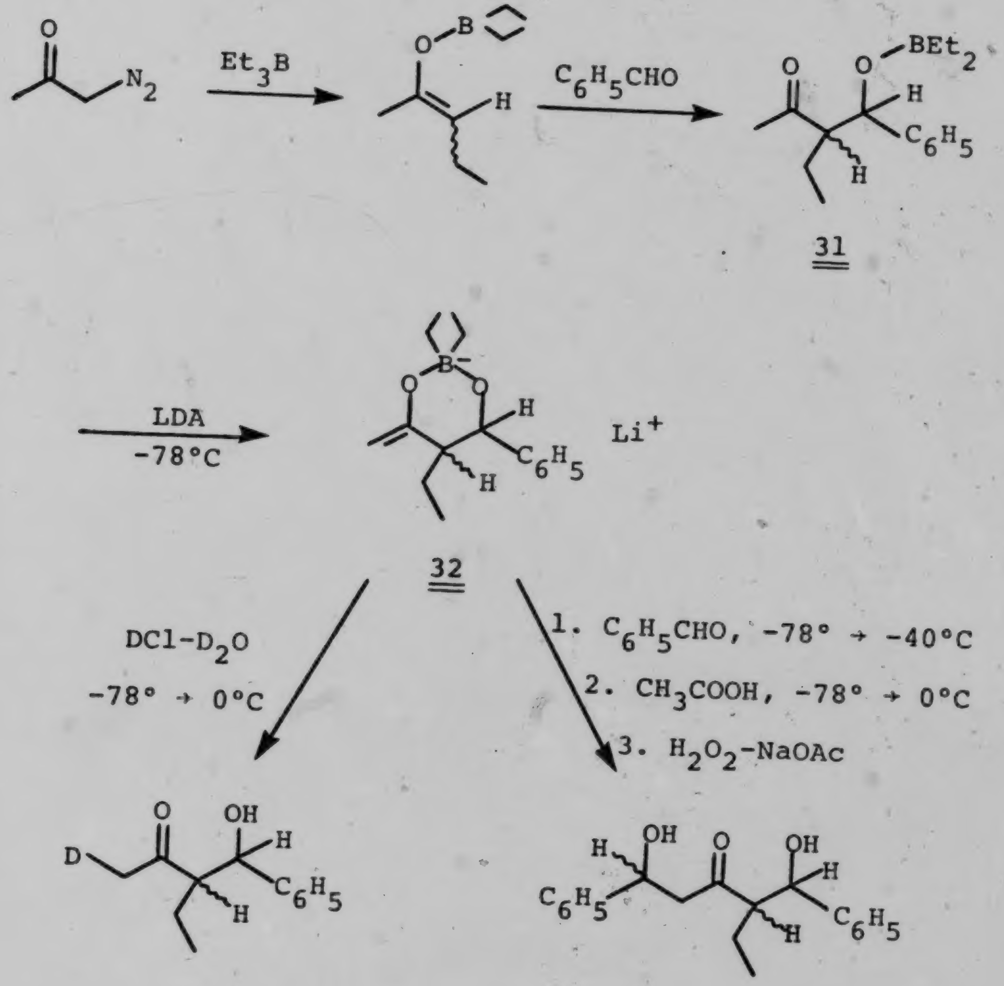
(56)

R = C_6H_5-; CH_3-

The use of lithium diisopropylamide was next explored. The internal enol borinate of 2-pentanone (from diazoacetone and triethylborane) was reacted with benzaldehyde to give the β-diethylboryloxy ketone 31 (Scheme VII). The crude mixture was then treated sequentially (-78°C) with (a) lithium diisopropylamide and (b) benzaldehyde, respectively, after which the reaction mixture was quenched with acetic acid. The resulting product mixture again proved to be rather complicated and NMR spectroscopy showed that considerable benzaldehyde had not been consumed. This indicated that either the initial proton abstraction step or the second aldol condensation reaction had not proceeded satisfactory. It was then verified that the enolate 32 was indeed formed under these conditions by deuterolysis experiments. The β-diethylboryloxy ketone 31 was added to LDA and subsequently quenched with DCl - D_2O at -78°C. A diastereomeric mixture of β-hydroxy ketones was isolated in which one deuterium was incorporated in the terminal methyl group as shown by NMR spectroscopy

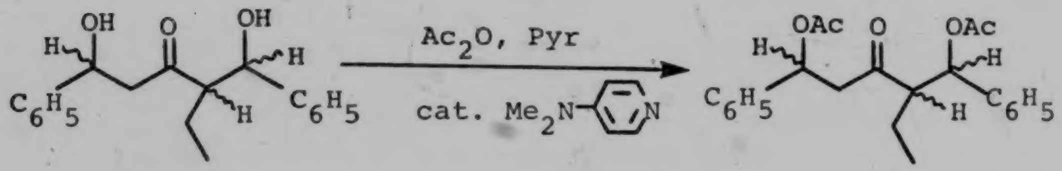
(Scheme VII).

Scheme VII


Et$_3$B
C$_6$H$_5$CHO
31
LDA
-78°C
Li$^+$
32
DCl-D$_2$O
-78° → 0°C
1. C$_6$H$_5$CHO, -78° → -40°C
2. CH$_3$COOH, -78° → 0°C
3. H$_2$O$_2$-NaOAc

Thus, proton abstraction had occurred cleanly in a highly regioselective manner and, importantly, this experiment showed that the boron-oxygen bond was apparently not cleaved by the amide base to any detectable extent. (The amide base would have been destroyed had it cleaved the boron-oxygen bond, thereby preventing enolate formation and subsequent deuterium incorporation). Apparently, the "enolate complex" was insufficiently reactive towards aldehydes at such low temperatures (-78°C), in contrast to normal lithium enolates. Repetition of the experiment at -30°C proved successful, since NMR spectroscopy now indicated disappearance of benzaldehyde, and loss of the terminal methyl group (δ 2.13, "threo" and 2.22 ppm, "erythro"). The latter observation indicated that the reaction had occurred regiospecifically at the terminal position.

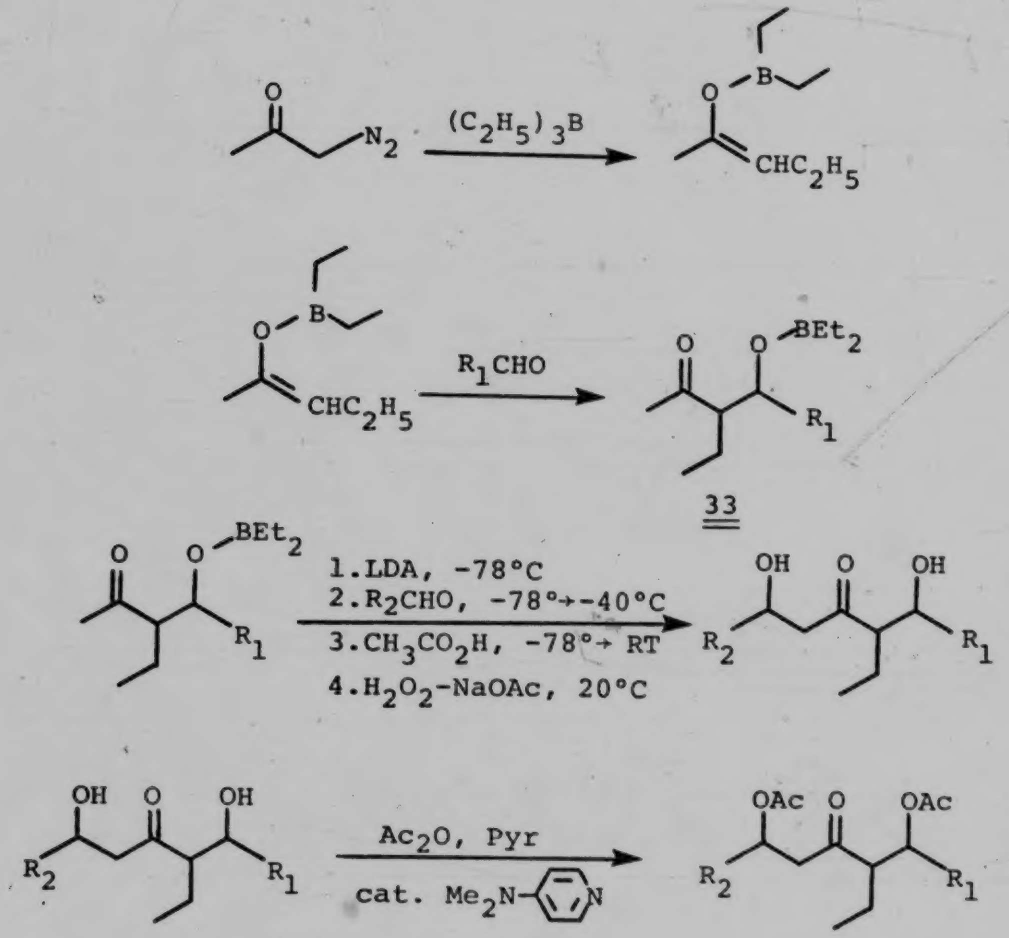
Isolation of the pure dihydroxy ketone proved difficult since either distillation or chromatography led to extensive retro aldol condensation and/or β-elimination resulting in the formation of α,β-unsaturated ketones. Attempts to crystallize the product failed as well. It was possible, however, to isolate the product as a diastereomeric mixture of diacetates by treatment with acetic anhydride and pyridine in the presence of a catalytic amount of 4-dimethylaminopyridine (eq. 57). This material crystallized nicely from a



(57)

mixture of ether and hexane. The absence of a methyl peak at ca. 2.1 ppm in the NMR spectrum showed again that the reaction had occurred regiospecifically.

This reaction can readily be applied to two different aliphatic aldehydes to afford unsymmetrical products in excellent yields (eq. 58). The reaction



O
N2
(C2H5)3B
O
B
CHC2H5
O
B
CHC2H5
R1CHO
O
O
BEt2
R1
O
O
BEt2
R1
1.LDA, -78°C
2.R2CHO, -78°→-40°C
3.CH3CO2H, -78°→ RT
4.H2O2-NaOAc, 20°C
OH
O
OH
R2
R1
OH
O
OH
R2
R1
Ac2O, Pyr
cat. Me2N-
N
OAc
O
OAc
R2
R1

(58a)

(58b)

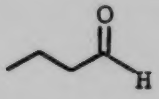
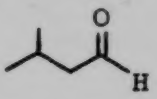
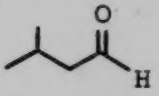
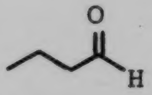
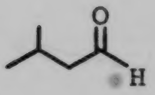
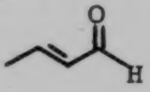
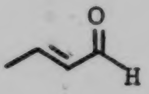
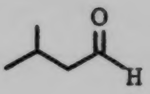
33

(58c)

(58d)

sequence also allows the synthesis of isomeric sets of mixed α,α'-di-aldol condensation products (Table XI, entries 2, 3, 4, and 5).

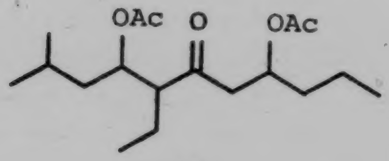
Table XI. Preparation of α,α'-Di-Aldol Condensation Products from α-Diazoacetone (Eq. 58)

entry	R_1CHO	R_2CHO	diacetate (%)
1	C_6H_5CHO	C_6H_5CHO	84
2			86
3			91
4			93
5			84

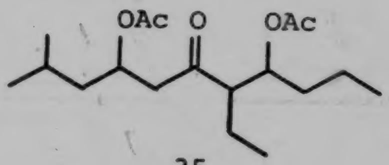
Thus, the β-diethylboryloxy derivative 33, (R_1 = $(CH_3)_2CHCH_2$), obtained by reaction of diazoacetone with triethylborane and isovaleraldehyde, respectively, was deprotonated (LDA) and then reacted with butyraldehyde. This produced diacetate 34 (91%) after acetylation (eq. 58). The isomeric diacetate 35 was synthesized analogously (86%), by introducing butyraldehyde and isovaleraldehyde in the reverse order.

Although 34 and 35 can be assigned structures on the basis of their method of synthesis, it is impossible to make an unambiguous structural assignment by NMR or infrared spectroscopy. In addition, these isomers are difficult to analyze by gas chromatography, even disregarding the presence of diastereomers.

However, mass spectral analysis allows a clear and unambiguous structure assignment of each isomer. The major fragmentation peaks arise from β-elimination resulting in the corresponding dienones, and from cleavage at the C-C bonds adjacent (α) to the carbonyl oxygen as illustrated in Scheme VIII. The high resolution mass spectra of both isomers show peaks corresponding to such fragmentation patterns, and results are indicated in Table XII. The major peaks of diacetate 34 are m/e: 199, 157, 139 (199-HOAc) and 97 (157-HOAc), while 35 shows m/e: 185, 171, 125 (185-HOAc) and 111 (171-HOAc). Although each compound has peaks of low intensity that correspond to the fragments of its isomer, such low intensity peaks can easily arise from a secondary hydrocarbon fragmentation pattern[142], resulting in the loss of methylene (C_nH_{2n}: 14, 28, etc.) groups. This process



34



35

Scheme VIII

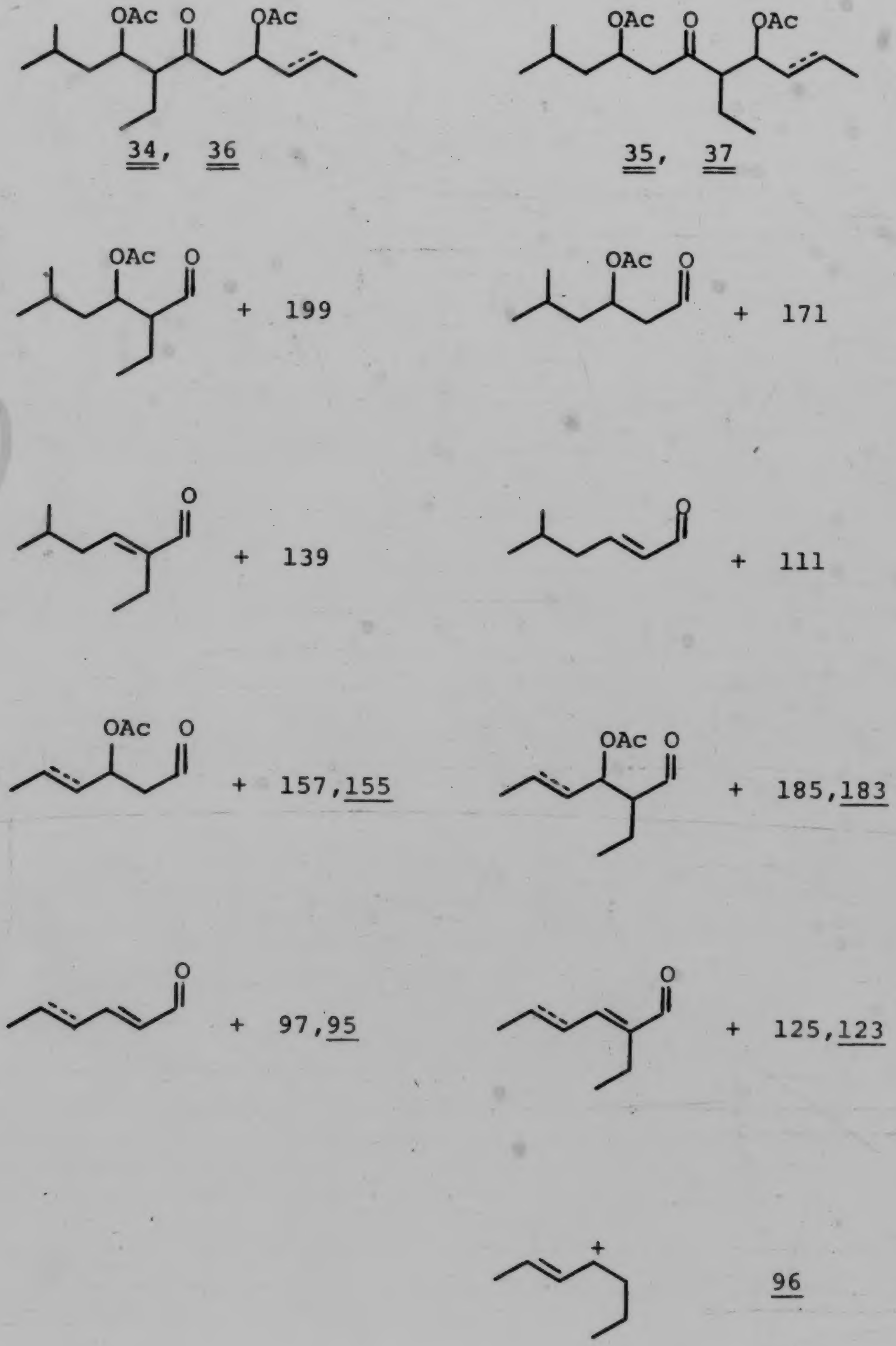

OAc
O
OAc
34, 36
OAc
O
OAc
35, 37
OAc
O
+ 199
OAc
O
+ 171
O
+ 139
O
+ 111
OAc
O
+ 157,155
OAc
O
+ 185,183
O
+ 97,95
O
+ 125,123
+
96

Table XII. Mass Spectral Data[a] for the Isomeric Set of 5- and 7-Ethyl Substituted 4,8-Diacetoxy-2-methylundecan-6-ones **34** and **35**

mass[b] (calcd)	mol formula	intensity (%)	
		34	**35**
328.2249	$C_{18}H_{32}O_5$	-	-
268.2038	$C_{16}H_{28}O_3$[c]	8.4	3.1
208.1828	$C_{14}H_{24}O$[d]	12.4	7.7
199.1334	$C_{11}H_{19}O_3$	14.1	-
185.1178	$C_{10}H_{7}O_3$	0.9	10.4
171.1021	$C_9H_{15}O_3$	4.0	36.8
157.0864	$C_8H_{13}O_3$	70.1	2.7
139.1123	$C_9H_{15}O$	61.1	3.1
125.0966	$C_8H_{13}O$	7.9	53.0
111.0810	$C_7H_{11}O$	15.9	100
97.0653	C_6H_9O	100	15.3

[a] At 70 eV; the samples were introduced at room temperature.

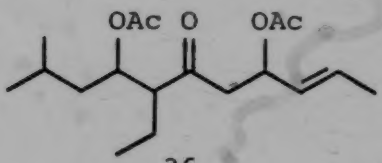
[b] The measured masses (m/e) were all within 0.0020 accuracy.

[c] M-HOAc.

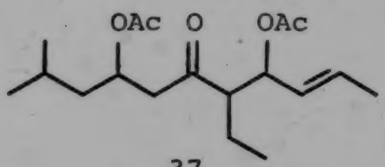
[d] M-2X HOAc.

becomes important in the corresponding dienones in which the consecutive loss of methylene units develops into a major fragmentation pattern (see Experimental section). It is of particular interest to note that the largest fragment from α-cleavage (m/e 199) is only present in diacetate 34 and completely absent in 35 !

Another isomeric set of mixed di-aldol products (i.e. the 5- and 7-ethyl substituted 4,8-diacetoxy-2-methyl-9-undecen-2-ones, Table XI, entries 4 and 5), was also prepared from diazoacetone, triethylborane, isovaleraldehyde, LDA and crotonaldehyde. The absence of an absorption in the NMR at δ 2.1 again indicated that these reactions had occurred regiospecifically at the terminal methyl group. The high resolution mass spectra of these isomeric diacetates 36 and 37 showed fragmentation peaks resulting from α-cleavage (Scheme VIII, dotted lines) and are summarized in Table XIII.



36



37

This process leads to major peaks of m/e: 199, 139 (199-HOAc) and 95 for diacetate 36, and m/e: 123, 111, and 96 for diacetate 37. As in the prior example, these

Table XIII. Mass Spectral Data[a] for the Isomeric Set of 5- and 7-Ethyl Substituted 4,8-Diacetoxy-2-methyl-9-undecen-6-ones 36 and 37

mass[b] (calcd)	mol formula	intensity (%)	
		36	37
326.2093	$C_{18}H_{30}O_5$	-	-
266.1882	$C_{16}H_{26}O_3$[c]	5.3	2.7
206.1671	$C_{14}H_{22}O$[d]	13.9	7.7
199.1334	$C_{11}H_{19}O_3$	28.1	-
139.1123	$C_9H_{15}O$	100	9.2
123.0809	$C_8H_{11}O$	5.6	43.3
111.0810	$C_7H_{11}O$	14.0	79.3
96.0936	C_7H_{12}	8.1	100
95.0497	C_6H_7O	54.7	17.4

[a] At 70 eV; the samples were introduced at room temperature.

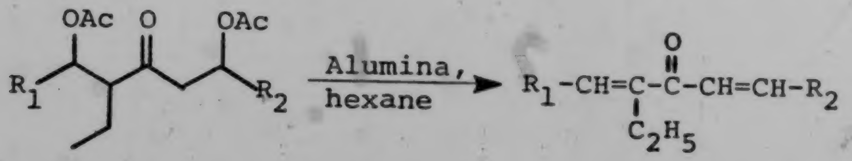
[b] The measured masses (m/e) were all within 0.0020 accuracy.

[c] M-HOAc.

[d] M-2X HOAc.

results show quite clearly that this synthesis leads to pure di-aldol condensation products (especially revealing is the complete absence of a peak at m/e 199 in 37.

The aliphatic diacetates were converted to the corresponding dienones and trienones by treatment with deactivated Alumina (activity III) as illustrated in equation 59. The use of more active Alumina (activity I or II) led to extensive polymerization. The unsaturated ketones were analyzed by conventional means (mass spectrometry, NMR, infrared and elemental analysis). The mass spectral data were again specially revealing for structural assignment of the different isomeric sets of dienones and trienones. Each isomer exhibited a characteristic fragmentation pattern, although these spectra were more complicated than those for the diacetates. This is due to the fact that dienones, and in particular trienones, show fragmentation patterns that are peculiar for hydrocarbons (see Experimental section). A number of peaks appear at intervals of 14 mass units caused by the consecutive loss of methylene groups[142]. For example, 5-ethyl-2-methyl-4,7-undecadien-6-one shows such a series of mass peaks, e.g. at m/e: 208 (12.7), 193 (4.9),



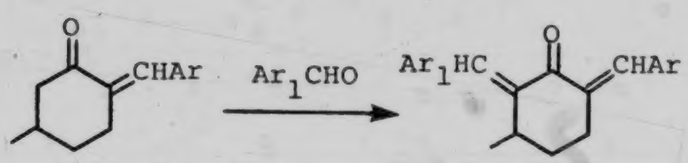
$$R_1\text{-CH=}\underset{C_2H_5}{C}\text{-}\overset{O}{\overset{\|}{C}}\text{-CH=CH-}R_2$$

(59)

179 (3.4), 165 (100) and 151 (10.8).

Thus, the assigned structure of the β,β'-diacetoxy ketones was further confirmed by analysis of the corresponding β-elimination products (dienones and trienones).

Despite the current active interest in aldol chemistry[143], no general method has as yet been reported for the preparation of di-aldols. Symmetrical α,α'-bis-aldol condensation products can be obtained by reacting symmetrical ketones (e.g. acetone, cyclopentanone, cyclohexanone and cycloheptanone) with two equivalents of an aromatic aldehyde in the presence of basic catalysts[135]. By starting with a monoarylidene cycloalkanone, aldol condensation with a different aldehyde can sometimes lead to unsymmetrical bis-arylidene cycloalkanones[135], as illustrated in equation 60.



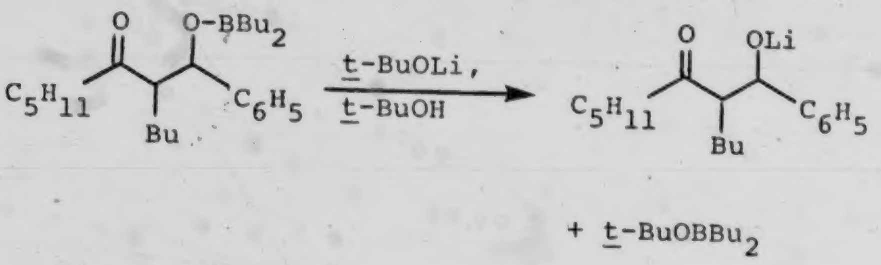
(60)

Ar = p-MeO-$C_6H_4^-$; Ar_1 = p-HO-C_6H_4.

This newly developed synthesis now makes it possible to synthesize β,β'-dihydroxy ketones comprised of two different enolizable aldehydes and aliphatic ketones in an unambiguous manner.

Having shown that β-dialkylboryloxy derivatives could be successfully aldolized after regiospecific generation of the *terminal* enolate complex **28**, the possibility of reversing the regiochemistry was briefly explored. The question arose whether the internal complex **28** could be equilibrated[6] to the internal enoxy borinate complex **29**. This appeared to be an attractive synthetic scheme since, if successful, both regioisomeric α,α'- and α,α-di-aldol products could be formed in this manner from the same intermediate β-dialkylboryloxy ketone. Toward this end, the intermediate β-dibutylboryloxy ketone **38** (obtained from reaction of 1-diazo-2-heptanone with tributylborane followed by benzaldehyde) was treated with lithium *tert*-butoxide (one equivalent) in *tert*-butyl alcohol at -78°C. After warming the mixture to 5°C and quenching with $DCl-D_2O$, the NMR spectrum of the isolated material showed *no* deuterium incorporation at either the methylene or methine carbon adjacent to the carbonyl group (Scheme IX).

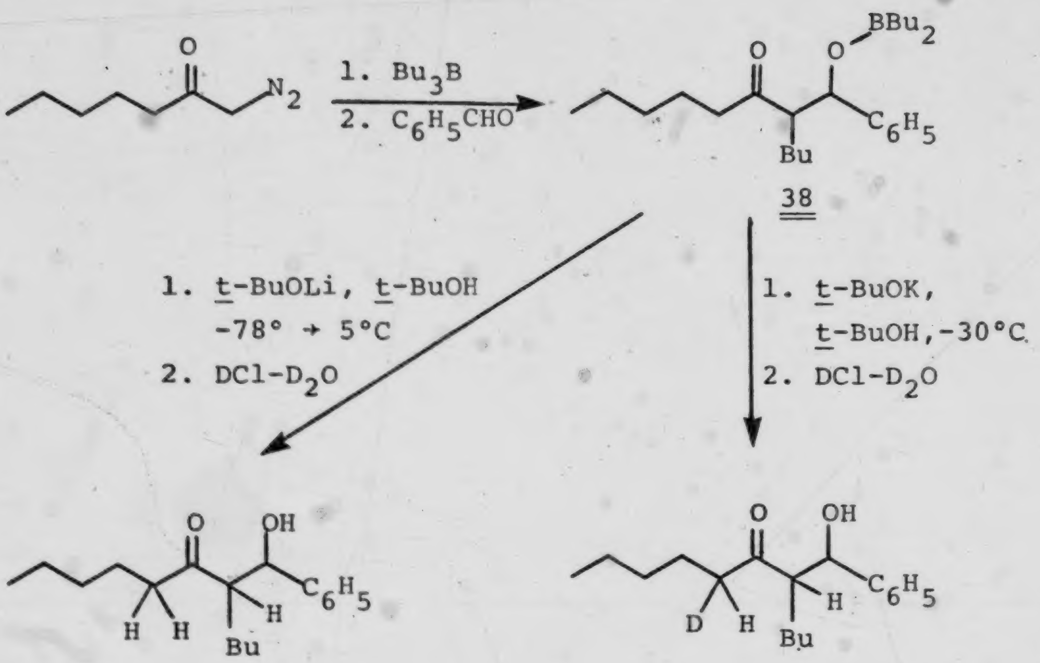
Apparently, either this base was insufficiently strong to accomplish proton abstraction under these conditions, or alternatively, attack at boron[91] could also have occurred (eq. 61) thereby destroying the



(61)

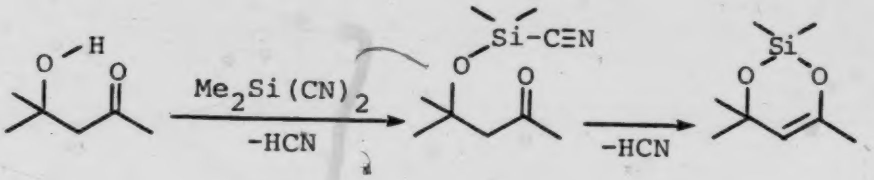
tert-butoxide base.

Scheme IX


N2
1. Bu3B
2. C6H5CHO
BBu2
O
C6H5
Bu
38
1. t-BuOLi, t-BuOH
-78° → 5°C
2. DCl-D2O
1. t-BuOK,
t-BuOH,-30°C
2. DCl-D2O
OH
H
D

The reaction was repeated with potassium tert-butoxide as base in tert-butyl alcohol/THF. After 1.5 hours at -30°C, deuterolysis afforded a β-hydroxy ketone that had incorporated a deuterium atom at the "exocyclic" methylene carbon (Scheme IX). Attempts to equilibrate this enolate to the isomeric internal enoxy borinate by stirring the mixture for prolonged time periods were not successful - the major product was an α,β-unsaturated ketone, resulting from β-elimination. Consequently, attempts to generate the more highly substituted internal enoxy borinate complex were discontinued.

Interestingly, however, a recent report described the regiospecific formation of an "endocyclic" enol silyl ether prepared from a β-hydroxy ketone[144]. Diacetone alcohol reacted with dimethyldicyanosilane to give the internal enol silyl ether regiospecifically as illustrated in equation 62. This reaction appears to involve the silylation of the alcohol as the first step, followed by addition of the cyanosilane across the carbonyl function and elimination of hydrogen cyanide.



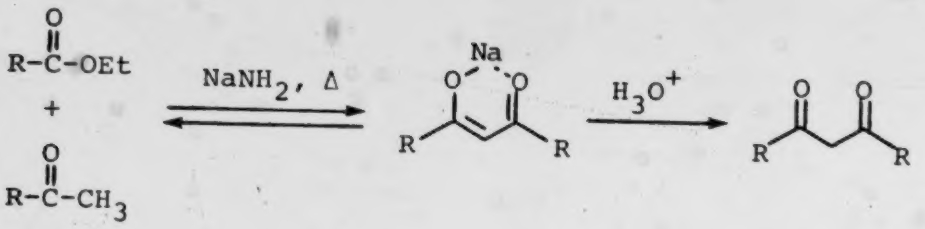
(62)

CHAPTER III

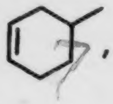
Synthesis of β-Diketones from Enol Borinates and Nitriles

The reaction of metal enolates with acylating reagents (e.g. acetyl chloride, acetic anhydride) is in general not suitable for the synthesis of β-diketones. Attack of the electrophile occurs predominantly at the oxygen of this ambident anion and the main product is usually an enol ester[6]. A few notable exceptions to this behaviour have recently been reported. Magnesium[31] and "organocopper"[41] enolates of certain cyclic ketones were found to give mainly C-acylation and only minor amounts of enol esters (eq. 37), although this ratio depends strongly on the nature of the solvent. Successful C-acylation in this instance is most reasonably attributed to the covalent character of the metal-oxygen bond of these enolates.

Ketone enolates also react with esters in a manner that is similar to the classical acetoacetic ester condensation.[26,145] For example, methyl isobutyl ketone condenses with ethyl isovalerate[146] in the presence of sodium amide to give, after acid hydrolysis, 2,8-dimethylnonane-4,6-dione (eq. 63, R = $(CH_3)_2CHCH_2-$). These reactions are controlled by a series of equilibria, and their success is attributed to the formation of a

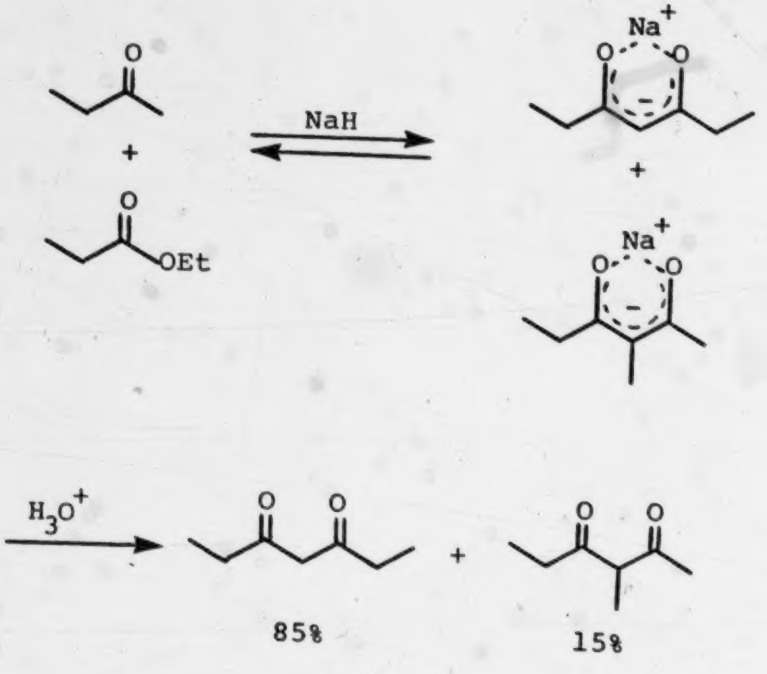


(63)

R = CH_3-, C_6H_5-, , $(CH_3)_2CHCH_2$-.

very stable β-keto enolate salt, which shifts the equilibrium to the desired product.[126,145]

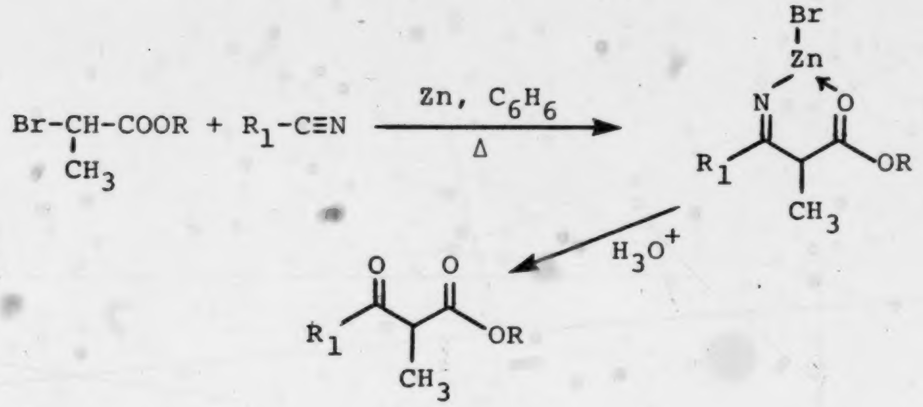
Methyl alkyl ketones are predominantly acylated at the less substituted site using this procedure[126,145-149]. For example, acylation of 2-butanone with ethyl propionate in the presence of base leads regioselectively to the centrally unsubstituted β-diketone (eq. 64)[149], and the substituted 3-methylhexane-



(64)

2,4-dione is only a minor component of the mixture. This preferential acylation has been attributed to be a reflection of the relative stability of the respective 1,3-dicarbonyl enolates rather than that of the starting (ketone) enolates[126,145].

Alternatively, it is possible in some cases to prepare β-dicarbonyl compounds (especially β-keto esters) by the reaction of ester enolates and nitriles, and this has been used in a modified Reformatsky reaction. Thus, an α-bromo ester,[150] after conversion to its bromozinc enolate and subsequent reaction with a nitrile, gives a β-keto ester upon hydrolysis (eq. 65).

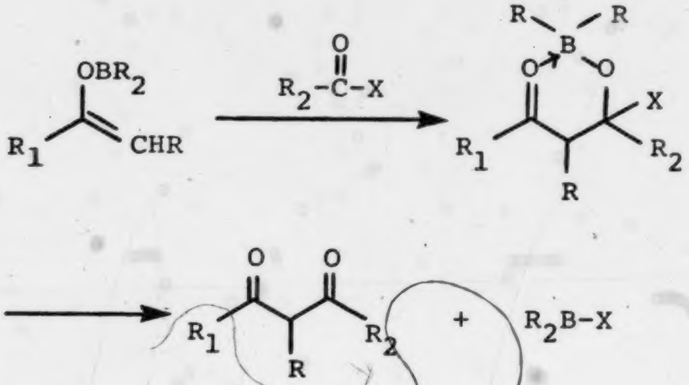


(65)

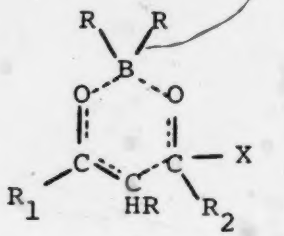
The success of this reaction has been attributed to the relatively slow equilibration of bromozinc enolates in non-polar solvents, and to the formation of a stable metal complex in which the metal is coordinated in a bidentate manner[126].

This reaction, however, is usually not applicable to α-bromo ketones since this often leads to self-condensation. Moreover, the regiospecific formation of α-bromo ketones is often difficult as discussed earlier (Chapter I).

Enol borinates appeared to offer a valuable alternative route towards the synthesis of β-dicarbonyl compounds. The covalent character of the boron-oxygen bond would possibly favour C-acetylation (as opposed to O-acetylation) using acid halides and anhydrides (eq. 66). Similar to the aldol condensation of enol


OBR2
R1
CHR
R2-C-X
O
R
R
B
O
O
X
R1
R2
R
O
O
R1
R2
R
+ R2B-X

(66)

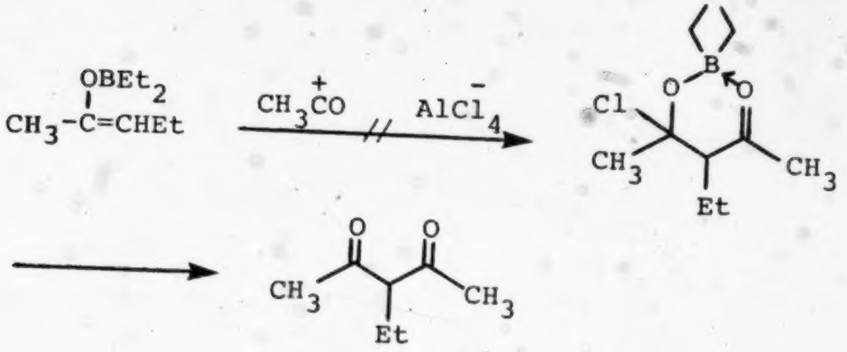

R
R
B
O
O
C
C
C
X
R1
HR
R2

39

borinates, an attractive six-membered transition state (39) can be postulated in which boron coordinates with the oxygen of the acylating reagent. Furthermore, the neutral reaction conditions would hopefully avoid the complications that plague the analogous metal enolate reactions.

Thus, diazoacetophenone was reacted with trihexylborane and the resulting enol borinate solution was treated with acetic anhydride at room temperature for several hours. After hydrolysis and oxidation (H_2O_2/NaOAc), GLC analysis indicated that the main product was heptyl phenyl ketone (from hydrolysis of the enol borinate). When more vigorous reaction conditions were employed a complicated mixture of products was obtained (as indicated by GLC analysis). Changing the nature of the acetylating reagent to acetyl bromide did not improve these results, and other enol borinates proved equally ineffective[151].

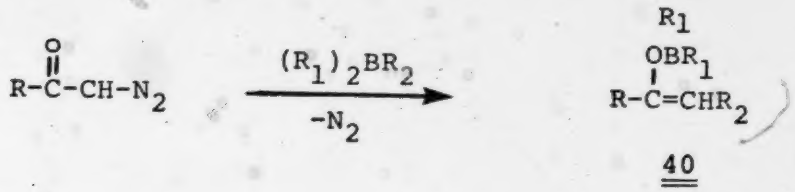
Olefins have been acetylated under Friedel-Crafts conditions by using acid chlorides and anhydrides, in the presence of Lewis acids, e.g. zinc chloride, boron trifluoride, and aluminum chloride[126]. The reaction of enol borinates with such a "Friedel-Crafts" reagent was thus attempted (eq. 67). Despite considerable efforts this reaction sequence did not prove successful, and resulted in a complex mixture of many unidentified products[151].



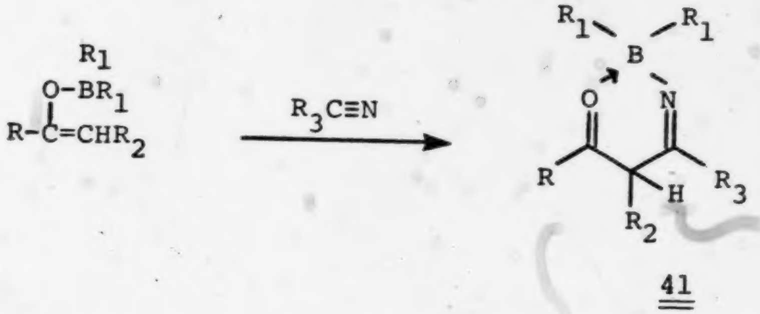
(67)

The acylation of enol borinates with nitriles was next attempted. Trialkylboranes are known to form stable coordination complexes with nitriles[152] and enol borinates were expected to form similar complexes. This would presumably activate the nitrile and simultaneously set the stage for the formation of a new carbon-carbon bond. Earlier observations about the strength of the boron-nitrogen bond prompted the expectation that nitriles would perhaps be effective as acylating reagents thereby producing a tetracoordinated boron intermediate 41, analogous to the previously mentioned zinc compound.

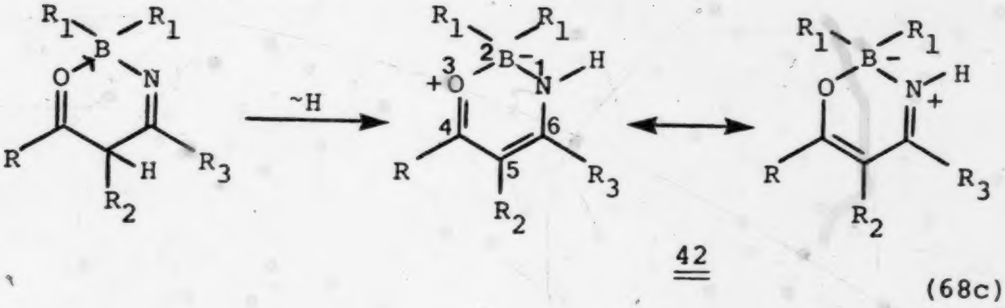
Thus, enol borinate 40 ($R = C_5H_{11}$, $R_1 = R_2 = C_2H_5$), prepared from 1-diazo-2-heptanone and triethylborane, was treated with heptanenitrile at room temperature and the mixture stirred overnight. The resulting yellow solution could not be hydrolyzed by brief treatment with 0.1 N HCl, nor could the expected β-diketone be isolated by attempted oxidation with hydrogen peroxide in aqueous sodium acetate. Column chromatography of the crude mixture provided a yellow oil that was identified as 2,2,5-triethyl-6-hexyl-4-pentyl-1H-boroxazine 42 ($R = C_5H_{11}$, $R_1 = R_2 = C_2H_5$) (eq. 68).


R-C(=O)-CH-N2
(R1)2BR2
-N2
R1
OBR1
R-C=CHR2
40

(68a)


R1
O-BR1
R-C=CHR2
R3C≡N
R1
R1
B
O
N
R
H
R3
R2
41

(68b)


R1
R1
B
O
N
R
H
R3
R2
~H
R1
R1
2
B
-
1
3
+O
N
H
4
6
5
R
R3
R2
42
R1
R1
B-
O
N+
H
R
R3
R2

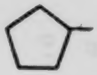
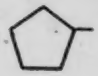
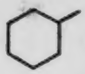
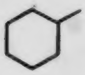
(68c)

Support for 42 was obtained spectroscopically by the presence of a broad resonance at δ ~5.8 in the NMR spectrum, by infrared absorptions at 3350 and 3400 cm^{-1} and by ^{11}B NMR and mass spectroscopy (see below). Although the mechanism for the formation of 42 has not been determined, a convenient rationale is the initial formation of 41 from enol borinate 40 and heptanenitrile (eq. 68b), followed by a proton shift from C(5) to N(1). Presumably, the driving force is the formation of an "aromatic (6π-electron) system, stabilized by resonance (eq. 68c).

Having thus established the feasibility of alkylating preformed enol borinates (40) with nitriles under mild and neutral conditions, the reaction was then explored for a variety of α-diazo ketones, organoboranes and nitriles. For example, sequential treatment of a solution of triethylborane with 1-diazo-2-heptanone in THF, followed (after nitrogen ceased to evolve) by addition of acetonitrile, afforded an 87% (isolated) yield of 1H-boroxazine 42 ($R = C_5H_{11}$, $R_1 = R_2 = C_2H_5$, $R_3 = CH_3$).

In most cases the yields were good (ca. 70-85%); the results are summarized in Table XIV. The lower yield of 2,2,5-tricyclopentyl-6-methyl-4-pentyl-1H-boroxazine (entry 4) is probably the result of steric hindrance in the initial reaction of the α-diazo ketone with the hindered tri-sec-alkylborane[98].

Table XIV. Synthesis of Substituted 1H-Boroxazines from Enol Borinates and Nitriles (Eq. 68)

entry	R	R_1	R_2	R_3	yield (%)[a]
1	C_5H_{11}	C_2H_5	C_2H_5	C_6H_{13}	35[b]
2	C_5H_{11}	C_2H_5	C_2H_5	CH_3	87
3	C_5H_{11}	C_4H_9	C_4H_9	C_2H_5	76
4	C_5H_{11}			CH_3	39
5	C_5H_{11}		H	CH_3	73
6	$(CH_3)_2CH$	C_4H_9	C_4H_9	CH_3	78
7		C_4H_9	C_4H_9	CH_3	70

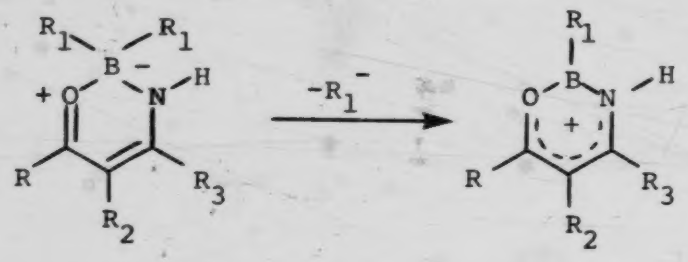
[a] Isolated yields.

[b] This yield was not optimized in this case.

Interestingly, terminal enol borinates, derived from α-diazo ketones and dicyclohexylborane, could be conveniently reacted at room temperature overnight to give a good yield of the corresponding 1H-boroxazine, despite the thermal instability of these enol derivatives (Chapter II).

All the boroxazines thus prepared show a rather remarkable resistance towards hydrolysis and oxidation, and are indefinitely stable under refrigeration (ca. 5°C); however, they appear to be oxidized (aerially?) in solution after a period of one to two weeks.

Rather extraordinarily, the mass spectra of these boron derivatives all exhibit only a single cluster of peaks. The fragmentation pattern results from the cleavage of the boron-carbon bond, which presumably leads to the formation of a stable "aromatic" fragment ion 43, as shown in equation 69. The molecular formula of this fragment was determined for all boroxazines by high resolution mass spectrometry and the results are summarized in Table XV. For example, 2,2,5-tributyl-6-ethyl-4-pentyl-1H-boroxazine (entry 3) exhibits a peak at m/e 292 which corresponds to the M-butyl ion fragment. The satellite peaks at m/e 291 and 293 arise from the respective ^{10}B and ^{13}C isotopes as verified by high resolution mass spectrometry.



43

(69)

Table XV. Mass Spectral Fragmentation Patterns of Substituted ^{1}H-Boroxazines[a] (Eq. 69)

entry[b]	R_1	$M-R_1$	m/e obs	m/e calcd
1	C_2H_5	$C_{18}H_{35}NO^{11}B$	292.2815	292.2812
2	C_2H_5	$C_{13}H_{25}NO^{11}B$	222.2031	222.2029
3	C_4H_9	$C_{18}H_{35}NO^{11}B$	292.2808	292.2812
4	C_5H_9	$C_{19}H_{33}NO^{11}B$	302.2650	302.2655
5	C_6H_{11}	$C_{15}H_{27}NO^{11}B$	248.2191	248.2185
6	C_4H_9	$C_{15}H_{29}NO^{11}B$	250.2344	250.2346
7	C_4H_9	$C_{18}H_{33}NO^{11}B$	290.2657	290.2659

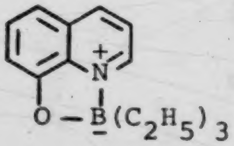
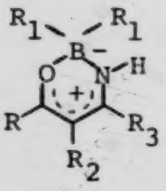
[a] At 70 eV, introduced at temperatures of 50-150°C.

[b] Entries 1-7 correspond with Table XIV.

Theoretically, the peak at m/e 292 can also result from cleavage of the alkyl group at C(5) of the boroxazine ring since R_1 and R_2 are the same in all but one case. However, the mass spectral data for 2,2,-dicyclohexyl-6-methyl-4-pentyl-1H-boroxazine (entry 5; $R_1 = C_6H_{11}$, $R_2 = H$) shows clearly that this does not occur, since the only fragmentation peak arises from the loss of a cyclohexyl group.

^{11}B NMR spectroscopy is an important probe for determining the coordination (i.e. trivalent or tetravalent) of a particular boron compound[153]. It can be seen from the chemical shift data for several organoboranes (Table XVI) that the electron density at boron strongly determines the position of ^{11}B resonances. Tetra-coordinated boron compounds, which carry a formal

Table XVI. ^{11}B NMR Chemical Shift Data of ^{1}H-Boroxazines and Representative Tri- and Tetra-Coordinated Boron Compounds[a,b]

boron compd (tri-coord)	δ	boron compd (tetra-coord)	δ
Me_3B	-86.8	$Li^+\ \overset{-}{B}Me_4$	+20.2
$Me_2B\text{-}OMe$	-53.0		-14.4
$PrCH{=}C(Me)OBEt_2$	-53.4		- 6
$Me_2N\text{-}BMe_2$	-44.6	$Me_3\overset{-}{B}\text{-}\overset{+}{N}Me_3$	+ 0.1

[a] References 49 and 153.

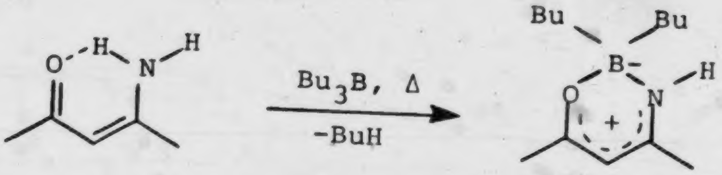
[b] Chemical Shifts in ppm relative to $BF_3 \cdot OEt_2$.

charge at boron, appear at considerably higher field (ca. -20 to +20 ppm for simple R_2BXY derivatives) than their tri-coordinated analogues (ca. -80 to -40 ppm). For example, trimethylborane absorbs at approximately 100 ppm lower field than lithium tetramethyl borate.

In addition to degree of coordination, the extent of electron density at the boron atom is influenced by the electronegativity and π-bonding abilities of each ligand. Thus, although both trimethylborane and methyl dimethylborinate are tri-coordinated, the boron ester absorbs at much higher field — this is attributable to the electron donating properties of the methoxy substituent.

The 1H-boroxazines (42) exhibit a broad resonance with a maximum at ca. 6 ppm downfield from boron trifluoride etherate which shows clearly that these boranes have a tetravalent character (Table XVI). Hence, the ^{11}B NMR spectral data also support the cyclic structure assignment of these compounds.

Several reports have appeared in the literature describing the formation of certain boroxazines[154,155]. For example, Hawthorne and Reintjes[155] found that 2,2-dibutyl-4,6-dimethyl-1H-boroxazine could be indirectly synthesized from 1,3-diketone derivatives, by reacting 2-imino-4-pentanone with tributylborane at elevated temperatures (eq. 70). They have also been obtained from



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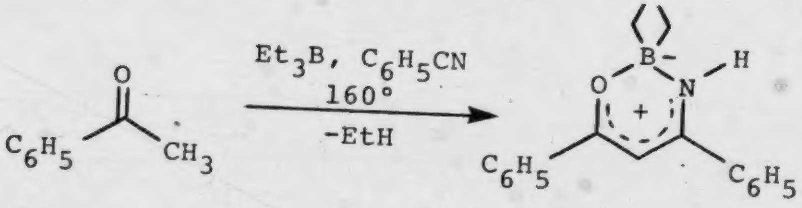


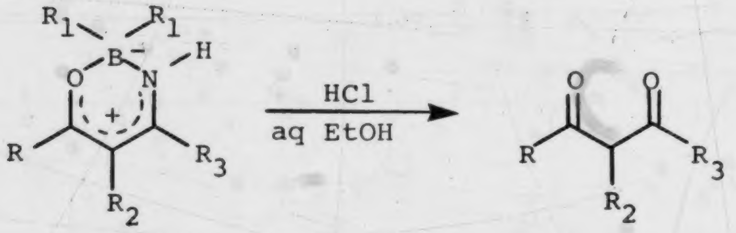
(71)

the thermal reaction of enolizable ketones, trialkylboranes and nitriles[156]. Thus, reaction of triethylborane, acetophenone and benzonitrile in an autoclave at 160°C for five hours afforded a 70% yield of 2,2-diethyl-4,6-diphenyl-1H-boroxazine (eq. 71).

However, these are vigorous and rather specialized conditions, and are probably unlikely to find general use as a route to 1,3-diketones. In addition, the process is obviously unsuitable for ketones that have two different enolizable sites and/or have the tendency to undergo self-condensation.

In contrast, our method can be conveniently employed as a one-flask reaction using ordinary "bench-top" techniques. Furthermore, the reaction occurs under mild (ca. 20 to 40°C) neutral conditions, and importantly, a variety of isomerically pure products can be unambiguously prepared in this manner.

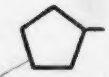
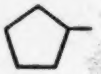
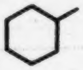
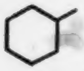
It was also demonstrated in the current investigation that all the boroxazines synthesized could be conveniently hydrolyzed employing aqueous ethanol in the presence of one or two equivalents of HCl. The reaction was easily monitored visually by noting the disappearance of the yellow colour of the boroxazine. The corresponding diketones could be isolated in nearly quantitative yield (eq. 72). For example, 2,2,5-tributyl-6-ethyl-4-pentyl-1H-boroxazine was refluxed (4 h) in 80% aqueous ethanol in the presence of ca. two equivalents of HCl to give a 93% isolated yield of 4-butyldecane-3,5-dione. The results are summarized in Table XVII.



(72)

Thus, the reaction of enol borinates with nitriles leads to excellent yields of β-ketones after acid hydrolysis. This method provides a flexible synthesis of such compounds. Regiospecifically generated terminal enol borinates (from α-diazo ketones and dicyclohexylborane) can be used to synthesize centrally unsubstituted β-diketones (entry 5). Such compounds[157] can also be

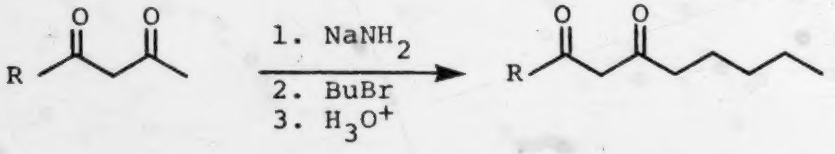
Table XVII. Formation of β-Diketones by Acid Hydrolysis of 1H-Boroxazines (Eq. 72)

entry	R	R_1	R_2	R_3	yield (%)[a]
1	C_5H_{11}	C_2H_5	C_2H_5	C_6H_{13}	-[b]
2	C_5H_{11}	C_2H_5	C_2H_5	CH_3	96
3	C_5H_{11}	C_4H_9	C_4H_9	C_2H_5	93
4	C_5H_{11}			CH_3	89
5	C_5H_{11}		H	CH_3	93
6	$(CH_3)_2CH$	C_4H_9	C_4H_9	CH_3	94
7		C_4H_9	C_4H_9	CH_3	95

[a] Isolated yields.

[b] Yield not determined.

prepared by alkylation of the dianion of symmetrical diketones (i.e. pentane-2,4-dione) or other mono-enolizable diketones using alkyl halides (eq. 73).



(73)

R = Me, C_6H_5.

However, the current method can be easily adapted for introducing two different substituents on both ends of the dicarbonyl system.

By using trialkylboranes, it is moreover possible to introduce simultaneously an acyl group and an alkyl group at the α-position of α-diazo ketones producing centrally substituted β-diketones (Table XVII, entries 1-4, 6 and 7). For example, 3-butylnonane-2,4-dione can be conveniently prepared in 85% overall yield in this manner. This is a useful device for preparing centrally alkylated β-diketones, since traditional methods - alkylation of the corresponding β-diketo enolate — is often severely hampered by the formation of O-alkylated products. The reaction is also applicable to the introduction of secondary alkyl groups at the central carbon of β-diketones (Table XVII, entry 4). The somewhat lower yield of this latter reaction is caused by the initial slow condensation of tricyclopentylborane and α-diazo ketones. Nevertheless, the simplicity and directness of the procedure render it an attractive alternative to direct alkylation of β-diketones since 2° halides undergo elimination, etc.

Sterically hindered α-diazo ketones, e.g. 1-diazo-3-methyl-2-butanone and 1-cyclohexyl-2-diazo-1-ethanone, also gave rise to very good yields of β-diketones.

In conclusion, this investigation has shown that the regiospecific construction of 1H-boroxazines can be achieved by the addition of nitriles to enol borinates. These species possess a cyclic structure as shown by spectroscopic studies. Furthermore, the boroxazines could be successfully employed in the regiospecific synthesis of β-diketones, providing access to compounds that are not easily available via other routes[158].

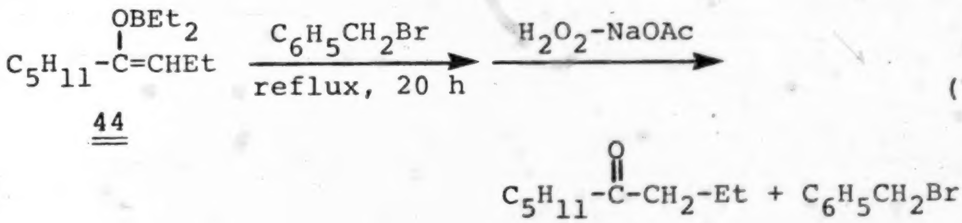
CHAPTER IV

Alkylation of Enol Borinates

As shown in earlier sections, enol borinates react cleanly with a range of reactive electrophiles (e.g. D_2O, "Mannich" reagents, aldehydes, ketones, nitriles and brominating reagents) leading to new, regioisomerically pure carbonyl derivatives. The next question examined was whether these intermediates could participate in alkylation reactions with simple alkyl halides, and, if this were indeed the case, whether this process would occur with retention of regiointegrity.

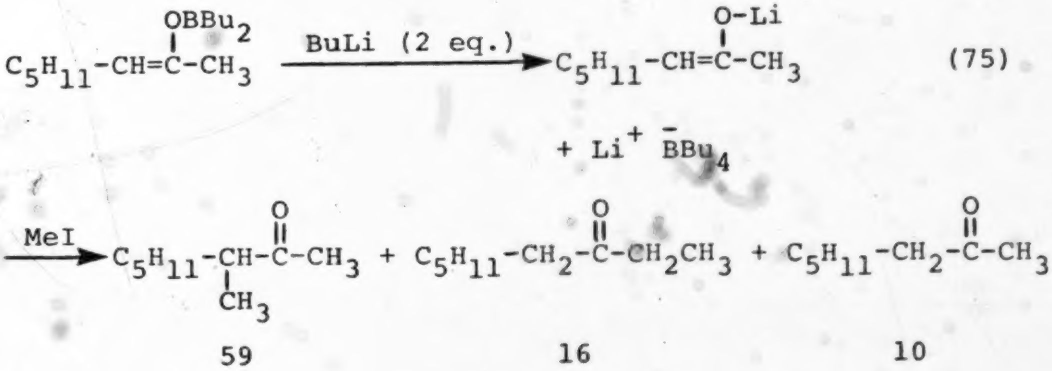
Much of the information available concerning direction of enol(ate) formation, enolate stabilities, and alkylation behaviour has been obtained on simple "model" substrates. For cyclic unsymmetric ketones, for example, 2-methylcyclohexanone is often employed as a "standard", (Table III), and in acyclic systems, a methyl alkyl ketone is frequently used for this purpose (Table IV). Analogously, in this study simple methyl alkyl ketone "equivalents" — $R_1CH{=}C(Me)OBR_2$ and $CH_2{=}C(R_1)OBR_2$ — were selected as models to establish whether alkylation could be accomplished regiospecifically either at the internal or terminal position.

It was quickly learned, however, that enol borinates are insufficiently reactive towards simple alkyl halides. For example, a solution of benzyl bromide and enol borinate 44 was refluxed in THF for 20 hours, but 4-nonanone (from 44) was the only product that could be isolated after hydrolysis (eq. 74).



$$\underset{\underline{\underline{44}}}{C_5H_{11}\text{-}\overset{\overset{\textstyle OBEt_2}{|}}{C}\text{=CHEt}} \xrightarrow[\text{reflux, 20 h}]{C_6H_5CH_2Br} \xrightarrow{H_2O_2\text{-NaOAc}} C_5H_{11}\text{-}\overset{\overset{\textstyle O}{\|}}{C}\text{-}CH_2\text{-Et} + C_6H_5CH_2Br \qquad (74)$$

Pasto and Wojtkowski[159] attempted to activate enol borinates by addition of n-butyllithium, and noted that two equivalents were required to optimize the yield of alkylated ketone. However, the enol borinate was presumably cleaved under these reaction conditions, resulting in the formation of the free lithium enolate and unreactive lithium tetrabutylborate. Upon subsequent reaction with an alkyl halide a mixture of isomeric alkylated ketones as well as hydrolyzed starting material (eq. 75) was obtained. These results are comparable



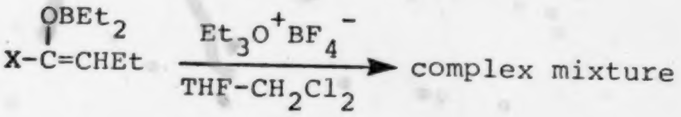
$$C_5H_{11}\text{-CH=}\overset{\overset{\textstyle OBBu_2}{|}}{C}\text{-}CH_3 \xrightarrow{\text{BuLi (2 eq.)}} C_5H_{11}\text{-CH=}\overset{\overset{\textstyle O\text{-}Li}{|}}{C}\text{-}CH_3 + Li^+\,\overset{-}{B}Bu_4 \qquad (75)$$

$$\xrightarrow{MeI} \underset{59}{C_5H_{11}\text{-}\underset{\underset{\textstyle CH_3}{|}}{CH}\text{-}\overset{\overset{\textstyle O}{\|}}{C}\text{-}CH_3} + \underset{16}{C_5H_{11}\text{-}CH_2\text{-}\overset{\overset{\textstyle O}{\|}}{C}\text{-}CH_2CH_3} + \underset{10}{C_5H_{11}\text{-}CH_2\text{-}\overset{\overset{\textstyle O}{\|}}{C}\text{-}CH_3}$$

to earlier studies on alkylation of lithium enolates (cf discussion in Section B, Chapter I).

Nonetheless, a number of observations in the field of enolate chemistry indicated that this approach was worthy of further investigation. For example, addition of triethylaluminum to the lithium enolates of cyclohexanones markedly diminished polyalkylation[160]. Secondly, unreactive enol silyl ethers were shown to undergo regioselective alkylation with simple alkyl halides in the presence of tetraalkylammonium fluoride, which served to activate the enol derivative[123,124] (eq. 32). Since enol borinates themselves are unreactive towards alkyl halides, two possibilities existed: either "activate" the carbon electrophile or, alternatively, convert the enol borinate into a more reactive form.

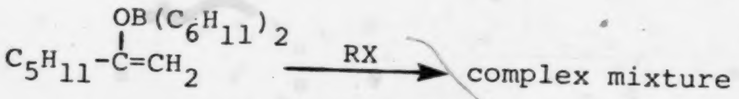
The reaction of enol borinates with more reactive electrophiles was first explored. Treatment of several enol borinates with triethyloxonium tetrafluoroborate (3 hours, room temperature) led to complicated reaction mixtures, which included hydrolyzed starting material (eq. 76)[151].



$$\text{X-}\overset{\overset{\text{OBEt}_2}{|}}{\text{C}}\text{=CHEt} \xrightarrow[\text{THF-CH}_2\text{Cl}_2]{\text{Et}_3\text{O}^+\text{BF}_4^-} \text{complex mixture} \qquad (76)$$

X = OEt, C_6H_5.

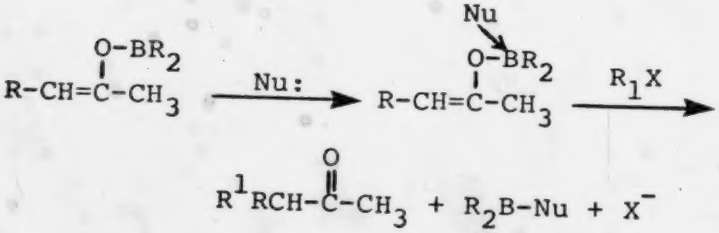
Attempts to react terminal enol borinates with either trimethylsulfonium, trimethylsulfoxonium or N-methylpyridinium iodide (eq. 77) also led to very complicated



$$C_5H_{11}-\overset{OB(C_6H_{11})_2}{\overset{|}{C}}=CH_2 \xrightarrow{RX} \text{complex mixture} \qquad (77)$$

$$RX = (CH_3)_3S^+\ I^-,\ (CH_3)_3\overset{+}{S}O\ I^-,\ C_5H_5\overset{+}{N}CH_3\ I^-.$$

mixtures, which contained none of the desired methylated ketones. This approach was therefore discontinued and efforts were subsequently directed towards finding a suitable way to "activate" the enol borinate.



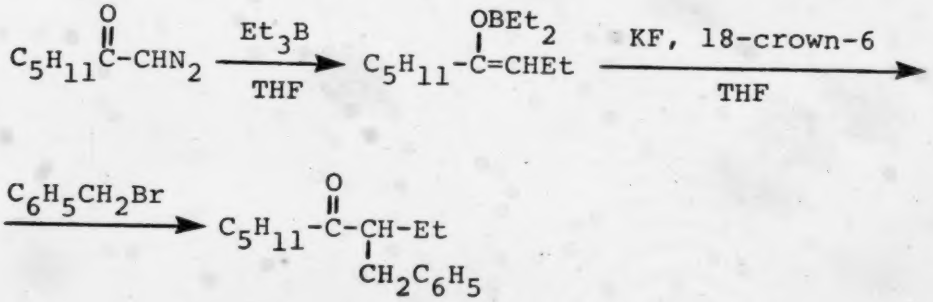
$$R-CH=\overset{O-BR_2}{\overset{|}{C}}-CH_3 \xrightarrow{Nu:} R-CH=\overset{\overset{Nu}{\searrow}O-BR_2}{\overset{|}{C}}-CH_3 \xrightarrow{R_1X} \qquad (78)$$

$$R^1RCH-\overset{O}{\overset{\|}{C}}-CH_3 + R_2B-Nu + X^-$$

The addition of various nucleophiles to an enol borinate was explored in an attempt to form such an activated tetra-coordinated "borate" complex. This would presumably weaken the boron-oxygen bond and facilitate electrophilic attack of alkyl halide (eq. 78). In fact, the successful aldol condensation and acylation reactions of enol borinates (Chapters II, III) can be attributed to a similar concept.

Initially, fluoride ion was investigated, since boron-fluorine bonds are known to be very strong. Addition of lithium fluoride to a solution of benzyl bromide and enol borinate 44 (from 1-diazo-2-heptanone and triethylborane) however, did not produce any benzylated ketone, but merely gave 4-nonanone upon hydrolysis. Although benzyltrimethylammonium fluoride has been shown to work well on enol silyl ethers[123,124] attempts to activate the enol borinate with this fluoride source gave unsatisfactory results.

The use of potassium fluoride and 18-crown-6 as additives was next examined (eq. 79). A mixture of enol



$$C_5H_{11}\overset{O}{\overset{\|}{C}}\text{-}CHN_2 \xrightarrow[THF]{Et_3B} C_5H_{11}\text{-}\overset{OBEt_2}{\overset{|}{C}}{=}CHEt \xrightarrow[THF]{KF,\ 18\text{-crown-6}}$$

$$\xrightarrow{C_6H_5CH_2Br} C_5H_{11}\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{CH_2C_6H_5}{\underset{|}{CH}}\text{-}Et \qquad (79)$$

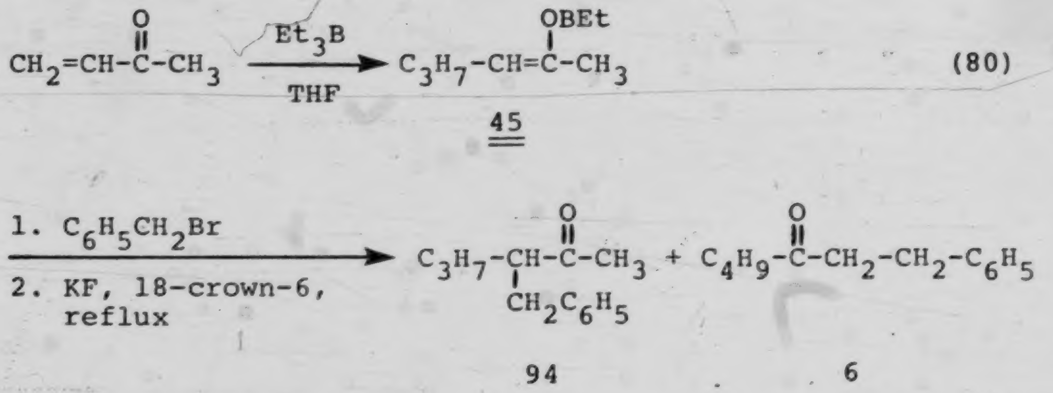
borinate 44, benzyl bromide, potassium fluoride and 18-crown-6, when refluxed in ether for several hours, resulted in the formation of some alkylated ketone (<20%). Changing the solvent to THF proved more promising (Table XVIII), and the α-benzylated nonanone(s) were produced in ca. 30% yield at room temperature. The yield of the alkylation product increased significantly (up to 75%) when the reaction was repeated in refluxing THF.

Table XVIII. Alkylation of Enol Borinates with Benzyl Bromide by Fluoride Ion Catalysis[a] (Eq. 79)

entry	reaction conditions time (h)	 temp	yield benzyl ketone (%)
1	48	r.t.	28
2	(a) 4	"	
	(b) 3	65°C	44
3	2.5	"	60
4	4	"	75
5	8	"	74

[a] KF, 18-crown-6 in THF.

Having thus established an effective method for alkylation, it was important to verify the regioselectivity. For analytical convenience, this was done by using the internal enol borinate of a methyl alkyl ketone since the two isomeric, benzylated ketones are easily separable (by GLC). Thus, enol borinate 45 was prepared via conjugate addition of triethylborane to methyl vinyl ketone and treated with benzyl bromide in the presence of KF and 18-crown-6. This produced a mixture of 3-benzyl-2-hexanone and 1-phenyl-3-heptanone in a ratio of 94:6 (eq. 80).



$$CH_2{=}CH{-}\overset{\overset{O}{\|}}{C}{-}CH_3 \xrightarrow[THF]{Et_3B} \underset{\underline{\underline{45}}}{C_3H_7{-}CH{=}\overset{\overset{OBEt}{|}}{C}{-}CH_3} \qquad (80)$$

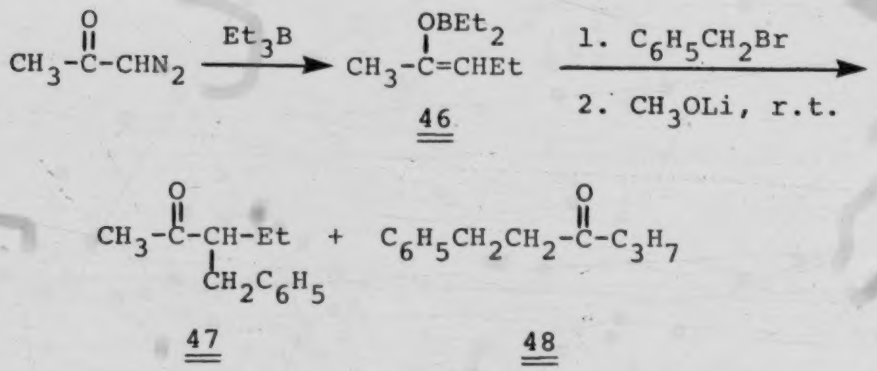
$$\xrightarrow[\text{2. KF, 18-crown-6, reflux}]{\text{1. } C_6H_5CH_2Br} \underset{94}{C_3H_7{-}\underset{\underset{CH_2C_6H_5}{|}}{CH}{-}\overset{\overset{O}{\|}}{C}{-}CH_3} + \underset{6}{C_4H_9{-}\overset{\overset{O}{\|}}{C}{-}CH_2{-}CH_2{-}C_6H_5}$$

The loss of regiointegrity observed in this fluoride-promoted procedure, was not promising in the light of a regiospecific alkylation, and this approach was consequently not further investigated.

Pyridine was also examined as an "activator", since various nitrogeneous bases are known to form stable coordination complexes with boranes[130]. For example, phenyl dibutylborinate[161] reacts with pyridine to produce a stable borane-amine adduct (mp 57°C). However, this proved ineffective as well for this purpose since only unalkylated ketone could be detected upon hydrolysis. Moreover, the pyridine appeared to have reacted with the alkyl halide in preference to the enol borinate (indicated by the disappearance of benzyl bromide in the organic residue).

The use of a mercaptide as a ligand gave similar results. Thus, addition of lithium butanethiolate to enol borinate 44, followed by addition of benzyl bromide did not lead to the desired product. NMR spectral data indicated that the alkylating reagent had reacted preferentially with the mercaptide to give benzyl butyl sulfide.

More promising results were obtained when lithium methoxide was used. Addition of enol borinate 46 to one equivalent of lithium methoxide followed by benzyl bromide (eq. 81) gave 3-benzyl-2-pentanone in good regioselectivity (47:48 = 98:2) but rather poor yield (30-34%).



$$CH_3-\overset{O}{\overset{\|}{C}}-CHN_2 \xrightarrow{Et_3B} CH_3-\overset{OBEt_2}{\overset{|}{C}}=CHEt \xrightarrow[\text{2. } CH_3OLi\text{, r.t.}]{\text{1. } C_6H_5CH_2Br}$$

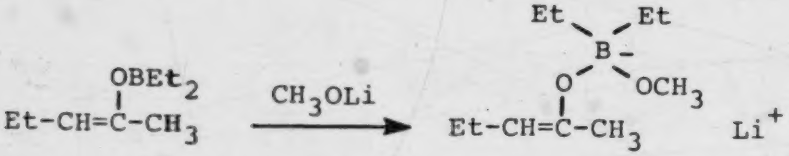
46

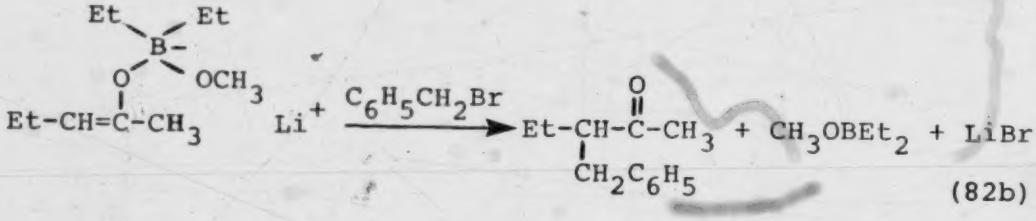
$$CH_3-\overset{O}{\overset{\|}{C}}-\underset{CH_2C_6H_5}{\underset{|}{CH}}-Et + C_6H_5CH_2CH_2-\overset{O}{\overset{\|}{C}}-C_3H_7 \qquad (81)$$

47 48

Somewhat higher yields of 3-benzyl-2-pentanone were obtained (ca. 50%) when two equivalents of lithium methoxide were employed, but this was now accompanied by more substantial amounts (8%) of the isomeric 1-phenyl-3-hexanone.

These results may be rationalized by assuming initial attack of lithium methoxide on the enol borinate to produce an enoxy borinate complex (eq. 82a). Benzylation of this complex would then lead to the benzylated ketone and methyl diethylborinate (eq. 82b),


(82a)

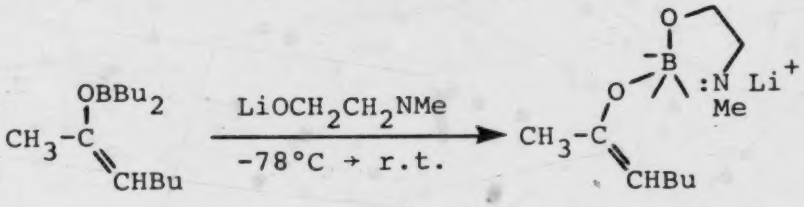

(82b)

$$CH_3OBEt_2 \xrightarrow{CH_3OLi} Et_2\bar{B}(OCH_3)_2\ Li^+ \qquad (82c)$$

the latter undergoing nucleophilic attack by a second equivalent of methoxide to form, yet another tetracoordinated "ate" complex (eq. 82c). However, any free methoxide present throughout the reaction course could also cause, the observed proton transfer.

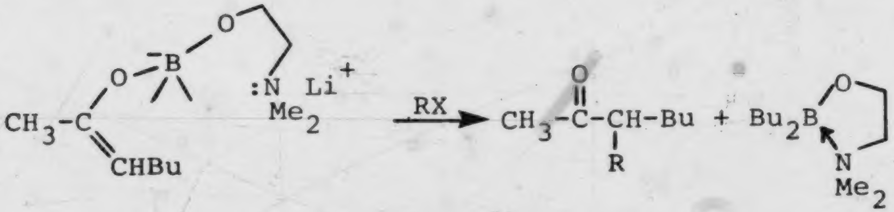
In the light of these results, it appeared desirable to replace the second equivalent of alkoxide by a less basic additive, which might also serve as a coordinating ligand for boron. The lithium salt of 2-(dimethylamino)ethanol was tested for this purpose, and ultimately proved to be the reagent of choice (eq. 83).

The lithium alkoxide was generated by addition of methyllithium to a solution of 2-(dimethylamino)ethanol in THF at 0-20°C. (Alkoxide formation could be followed by measuring the gas evolution or, more conveniently,


OBBu2
CH3-C
CHBu
LiOCH2CH2NMe
-78°C → r.t.
O
B
:N Li+
Me
O
CH3-C
CHBu

(83a)

49


O
B
O
:N Li+
Me2
CH3-C
CHBu
RX
O
CH3-C-CH-Bu
R
+ Bu2B
O
N
Me2

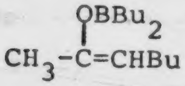
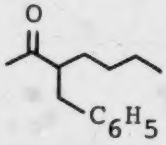
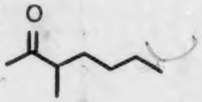
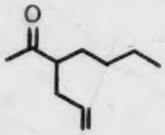
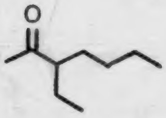
(83b)

by using triphenylmethane as an indicator.) A solution of the enol borinate 49 — prepared in situ from diazoacetone and tributylborane — and an alkyl halide was then added to the cooled (-78°C) suspension. The precipitate dissolved in ca. 5 to 10 minutes at room temperature and the reaction was usually complete after several hours.

The reaction was performed with several representative alkyl halides and the yields were in general very good. The results are summarized in Table XIX. Benzylation, methylation and allylation resulted in yields ranging from ca. 75-90%, while reaction with ethyl iodide gave a somewhat lower yield (presumably due to the diminished reactivity of this electrophile).

Importantly, all these reactions produced the alkylated ketones regiospecifically, and the corresponding regioisomers could not be detected by GLC

Table XIX. The Regiospecific Alkylation of Internal Enol Borinates with Representative Alkyl Halides in the Presence of Lithium 2-(Dimethylamino)ethanolate (Eq. 83)

enol borinate	RX	product	yield[a] (%)
 $CH_3-\overset{OBBu_2}{C}=CHBu$	$C_6H_5CH_2Br$		76 (70)
	MeI		88
	Me_2SO_4		82
	$CH_2=CH-CH_2Br$		75
	EtI		49

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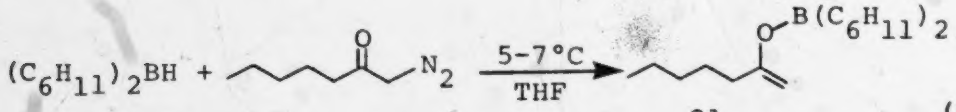
[a] Determined by GLC analysis; isolated yields in parentheses.

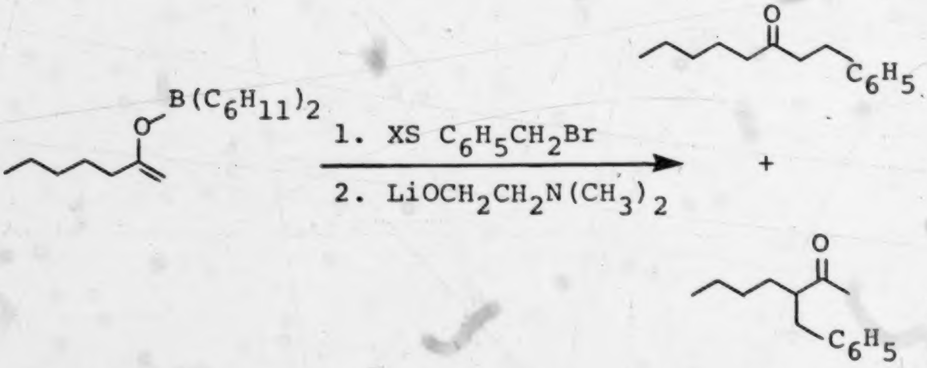
analysis ! However, small amounts of isomeric alkylation products (1-2%) could be found if the amount of lithium 2-(dimethylamino)ethanolate exceeded that of the trialkylborane employed.

Since alkylation of internal enol borinates proved successful, the alkylation of the corresponding terminal derivatives was next investigated. Enol borinate 21 (from 1-diazo-2-heptanone and dicyclohexylborane) was treated in situ with benzyl bromide and lithium 2-(dimethylamino)ethanolate at room temperature for several hours. A complicated, difficultly separable mixture was obtained that contained ca. 15% of the benzylated 2-heptanones. The undesired regioisomer predominated (eq. 84) in approximately a ratio of 3:1.


(C6H11)2BH +
O
N2
5-7°C
THF
O
B(C6H11)2

21

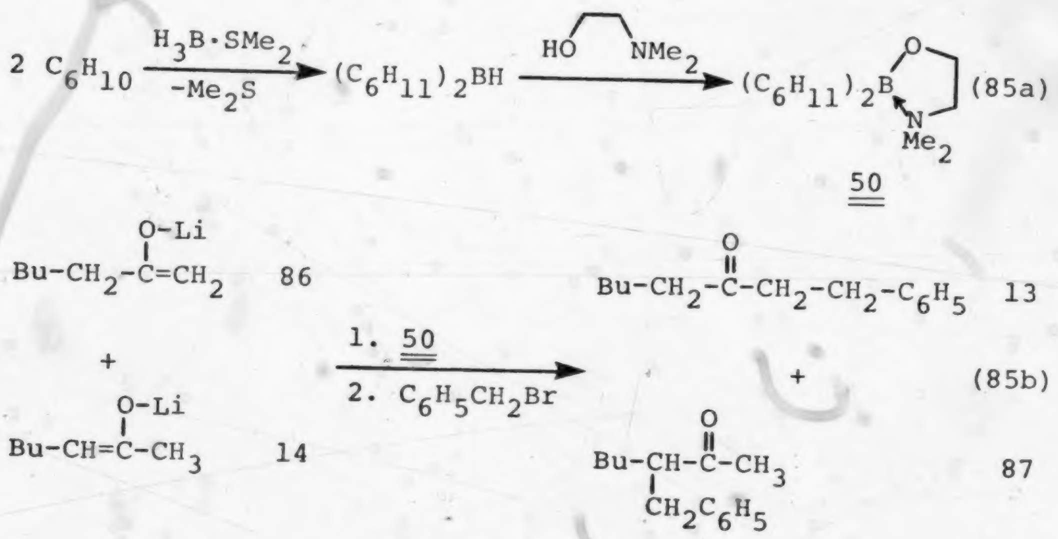
(84a)


O
B(C6H11)2
1. XS C6H5CH2Br
2. LiOCH2CH2N(CH3)2
O
C6H5
24%
+
O
C6H5
76%

(84b)

This is presumably another example of base-induced proton transfer analogous to results obtained in traditional base-catalyzed alkylation.

Alternative alkylation experiments were also attempted, involving the (presumed) borate complex generated by an independent synthesis (eq. 85).


2 C_6H_{10}
$H_3B\cdot SMe_2$
$-Me_2S$
$(C_6H_{11})_2BH$
HO
NMe_2
$(C_6H_{11})_2B$
O
N
Me_2
(85a)
50
O-Li
$Bu-CH_2-C=CH_2$
86
+
O-Li
$Bu-CH=C-CH_3$
14
1. 50
2. $C_6H_5CH_2Br$
O
$Bu-CH_2-C-CH_2-CH_2-C_6H_5$
13
+
(85b)
O
$Bu-CH-C-CH_3$
$CH_2C_6H_5$
87

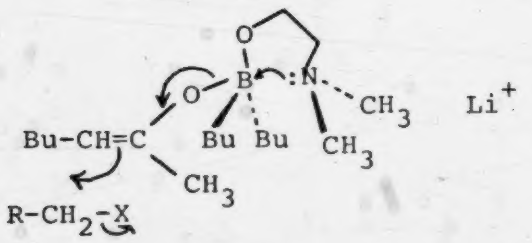
Dicyclohexylborane was reacted with 2-(dimethylamino)-ethanol (0-20°C) to produce 2-(dimethylamino)ethyl dicyclohexylborinate (50); the reaction could be easily monitored by the disappearance of the borane precipitate and simultaneous quantitative gas evolution (H_2).

This intermediate (50) was then treated with the mixture of lithium enolates (86:14, terminal-internal) of 2-heptanone derived from two independent experiments, followed by reaction with benzyl bromide. In one, the solution of lithium enolates obtained from direct kinetic deprotonation with lithium diisopropylamide was employed[9]. In the second experiment, these lithium enolates were converted to their enol trimethylsilyl ether derivatives, isolated by distillation, and independently regenerated by treatment with methyllithium.

Unfortunately in either case, the alkylation experiments produced a mixture of benzylated 2-heptanones in low yield (ca. 30%) in which the undesired regioisomer predominated in a ratio of 87:13 (eq. 85b). Further attempts to regiospecifically alkylate terminal enol borinates were therefore discontinued, and it remains for future investigations to develop adequate procedures.

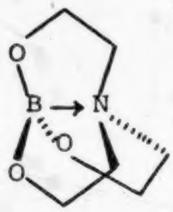
However, this investigation has shown that internal enol borinates can be successfully monoalkylated with simple alkyl halides in a regiospecific manner in serviceable yields, when a suitable alkoxide was used as an additive. Although precise mechanistic details of this alkylation are not known, it is clear that "free" lithium enolates are not involved, since these species are known to induce proton transfer and all the problems associated with it (Chapter I, Section B). One possibility is the concerted alkylation of an "enoxy borinate" complex (Scheme XXIII), in which no residual concentra-

Scheme XXIII



tion of basic enolate is available for proton transfer and other side reactions. Additionally, the formation of a stable tetra-coordinated borate by-product may contribute to the mild regiospecific alkylation procedure.

A similar observation has also been made very recently[162,163] on the monoalkylation of metal enolate — e.g. Li^+, Na^+ and K^+ — using analogous procedures described in the current work. Rathke and Lindert[162] found that methylation of lithium and sodium enolates of cyclohexanone resulted in high yields of monoalkylation products upon prior addition of triethylborane or triethanolamineborate 51. It was postulated that this reaction may function by coordination of the borane (51) with the ketone enolate, thereby producing an intermediate enoxy borinate complex. Interestingly similar addition of other boron esters, such as trimethyl- and tri-*tert*-butylborate completely stopped the alkylation reaction.



51

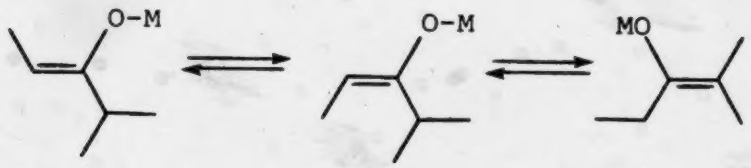
This approach has solved some of the problems encountered in the alkylation of unsymmetric cyclic ketones. However, the procedure has not yet been tested for the more demanding unsymmetric acyclic ketone enolates.

CHAPTER V

Stereoselective Formation of Enol Borinates

Although many methods are available for the generation of regioisomerically pure enol(ate)s (Chapter I) the stereoselective preparation of enol derivatives presents another more difficult problem. Recently several research groups have become actively involved in stereochemically controlled aldol condensation reactions through the initial stereoselective formation of enolates[50,164-168].

Regioisomeric and stereoisomeric ratios of enolates and enol derivatives derived from 2-methyl-3-pentanone have been examined in some detail by several authors[6,9,10,50] as shown in Table XX. These ratios are believed to reflect equilibrium conditions (eq. 86). For example, the reaction of 2-methyl-3-pentanone with potassium triphenylmethide under these conditions (i.e. excess proton donor) results in a 74:14 mixture of the geometrically isomeric Z- and E-type enolates (52a and 52b), whereas lithium triphenylmethide gave almost exclusively the Z-isomer 52a. Equilibrium mixtures of enol derivatives of this ketone (M = $SiMe_3$, Ac, Et and BEt_2) also consist of greater amounts of the Z-type isomers relative to the corresponding geometric E-isomers. Kinetic deprotonation with lithium diisopropylamide led



52a 52b 52c

(86)

Table XX. Stereoisomeric (and Regioisomeric) Distribution of Enolates and Enol Derivatives of 2-Methyl-3-pentanone (Eq. 86)

M	stereoisomeric distribution (%)		
	52a (Z)	52b (E)	52c (%)
K[a]	74	14	12
Li[a]	>98	<1	<1
Li[b]	42	53	5
$\mathrm{SiMe_3}$[a]	31	6	63
Ac[a]	42	3	55
Et[a]	32	13	55
$\mathrm{BEt_2}$[c]	90	10	--

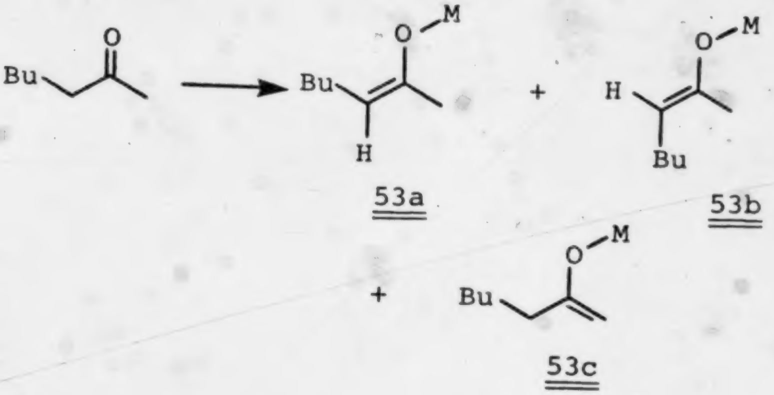
[a] Equilibrium conditions (ref. 6, 9 and 10).

[b] Kinetic deprotonation with LDA (ref. 9).

[c] Reaction of 2-methyl-3-pentanone with triethylborane (ref. 50).

to a ca. 1:1 mixture of 52a (Z) and 52b (E).

Very similar results have been obtained for the enol(ate)s of 2-heptanone[6,9,10] as shown in Table XXI.



(87)

Table XXI. Stereoisomeric (and Regioisomeric) Distribution of Enolates and Enol Derivatives of 2-Heptanone (Eq. 87)

M	stereoisomeric distribution (%) 53a (Z)	53b (E)	53c (%)
K[a,b]	39(46)	10(12)	51(42)
Li[a]	ca. 65	ca. 22	ca. 13
Li[c]	7	9	84
$SiMe_3$[a]	58	29	13
Ac[a]	69	28	3

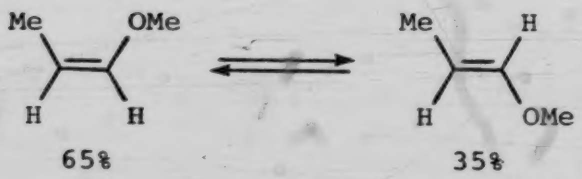
[a] Equilibrium conditions (ref. 6).

[b] References 6 and 10.

[c] Kinetic deprotonation with LDA (ref. 9).

Upon enolization under equilibrium conditions, the metal enolates (M = K, Li) and enol derivatives (M = $SiMe_3$, Ac) of this particular ketone were predominantly present as the Z-isomer 53a, whereas the corresponding geometrically isomeric E-enol(ate)s were only formed in minor amounts (eq. 87).

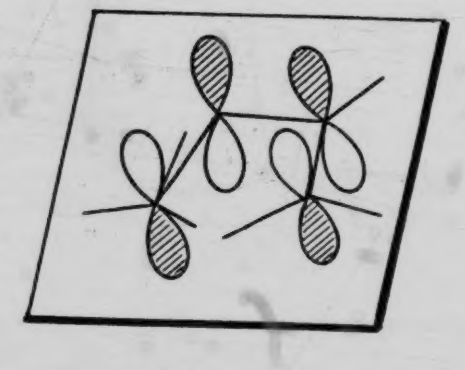
In addition, simple enol ethers, such as the isomeric 1-methoxy-1-propenes[169], display a stereochemical preference for the Z-isomer (eq. 88).



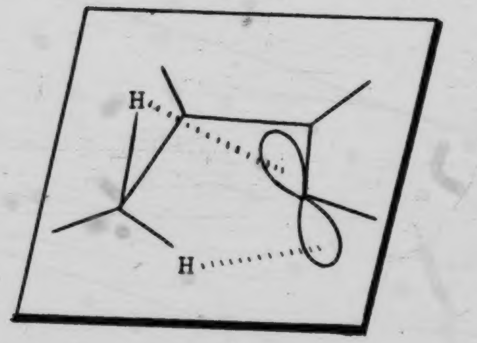
(88)

Since the Z-isomer in all these cases would appear to be the more sterically hindered of the two, the greater stability of Z- over E-isomers is not readily explicable on the basis of "steric effects".

The observed preference must mainly be attributed to attractive forces between the alkyl groups and the electron-rich heteroatom substituent. Their origin can be rationalized by a symmetry-allowed hyperconjugative π-interaction[170] as shown in 54. Alternatively, it has also been described as being the result of stabilizing intramolecular hydrogen bonding between the alkyl groups and the electron-rich 1-substituted heteroatom[171] as shown in 55.



54



55

Because of the active interest in stereochemically controlled enol(ate) formation, several enol borinates were examined for their ratio of geometric isomers. Thus, methyl vinyl ketone was reacted with tributylborane and the enol borinates were isolated by distillation (eq. 89). NMR analysis showed the presence of both the isomeric (E)- and (Z)-dibutyl(2-octen-2-yloxy)boranes, with triplets of quartets for the vinylic protons at δ 4.55 ($J = 7.0$, $J = 1$ Hz) for the Z-isomer, and at δ 4.67 ($J = 7.5$, $J = 1$ Hz) for the E-isomer. The ^{13}C NMR spectrum also showed the presence of at least two stereoisomers with peaks at δ 148.4 (2 peaks) for C(α), and 110.1 (Z) and 111:4 (E) for C(β). The E and Z enol borinates were formed in a ratio of ca. 2:3 in favour of the Z-isomer, and these results are similar to those obtained by Köster and coworkers[51].

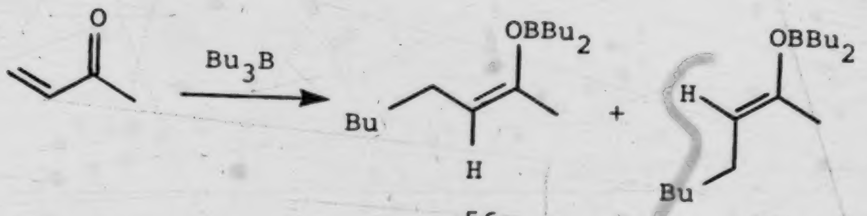
The stereochemical assignments of E and Z enol derivatives[172] are based on the NMR spectral correlation published earlier for olefinic protons of this type.

Vinylic protons of simple aliphatic enol derivatives with the E-geometry absorb invariably at lower field than the corresponding Z-isomer.

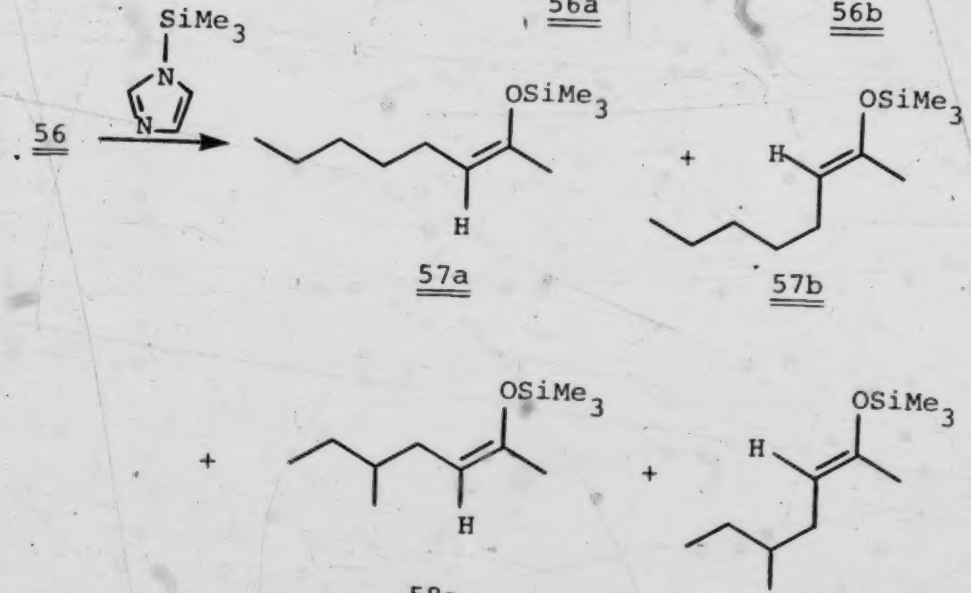
Although spectroscopic data showed the presence of both stereoisomeric enol borinates, the complete composition of the reaction mixture was not revealed by this method of analysis. Commercial tributylborane (Callery) is prepared via hydroboration of 1-butene. This places 94% of the boron in the 1-position and 6% in the 2-position. However, the overall organoborane composition consists of a statistical mixture of 83% tri-n-butylborane, 16% di-n-butyl-sec-butylborane, 1% n-butyl di-sec-butylborane, and a trace of tri-sec-butylborane[173].

For example, reaction of tributylborane (prepared via this route) with methyl vinyl ketone leads to a mixture of 2-octanone and 5-methyl-2-heptanone upon hydrolysis, in an 85:15 ratio[46]. The conjugate addition of organoboranes to α,β-unsaturated carbonyls was found to be a radical reaction and thus, not unexpectedly, secondary alkyl groups possess a greater migratory aptitude.

It was expected therefore, that the mixture of enol borinates prepared via this route was composed of two sets of geometrically isomeric enol borinates: (E/Z)-dibutyl-(2-octen-2-yloxy)borane and (E/Z)-dibutyl(5-methyl-2-hepten-2-yloxy)borane. However, enol borinates cannot easily be


O
Bu_3B
$OBBu_2$
Bu
H
H
$OBBu_2$
Bu

56a 56b (89)


$SiMe_3$
N
N
56
$OSiMe_3$
H
57a
$OSiMe_3$
H
57b
$OSiMe_3$
H
$OSiMe_3$
H

(90)

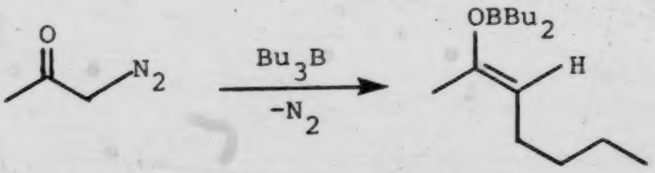
58a 58b

analyzed by GLC methods, because of their hydrolytic instability.

Consequently, exchange of the dibutylboryl group by a trimethylsilyl substituent was next examined. Treatment of 56 with N-trimethylsilylimidazole at room temperature (exothermic) afforded a mixture of enol silyl ethers (eq. 90). ^1H NMR spectroscopy showed the presence of the geometrically isomeric 57a (Z) and 57b (E) in a ratio of ca. 3:2 in favour of the Z-isomer. The vinylic proton of 57a absorbed at δ 4.40 (t, J = 6.4 Hz) and that of 57b at δ 4.62 (t, J = 6.7 Hz). The similar ratio of the E- and Z-isomers before and after silylation indicated that the conversion had occurred stereospecifically.

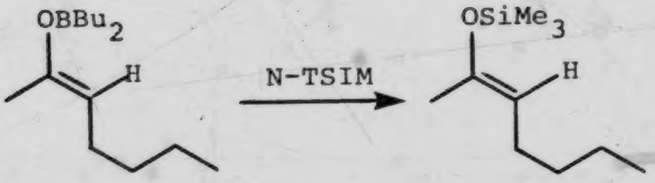
However, GLC analysis[9] gave a more accurate representation of the composition of the reaction mixture, and the structurally isomeric enol silyl ethers, resulting from the transfer of a sec-butyl group, could now also be detected. The isomers eluted in the following order: 58a (7%), 58b (5%), 57a (57%) and 57B (31%).

The reaction of diazoacetone and tributylborane (eq. 91) was next examined and this led to a rather



59b

(91)



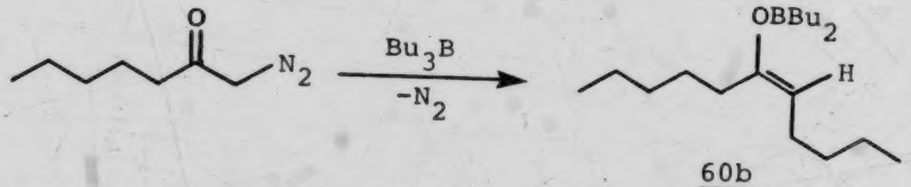
(92)

surprising discovery. NMR (^1H and ^{13}C) spectroscopy showed the presence of a single geometric isomer, (E)-dibutyl (2-hepten-2-yloxy)borane, with a vinylic proton absorption at δ 4.45 (tq, J = 7.5, J = 1 Hz) and a methyl absorption at δ 1.58 (d, J = 1 Hz). Treatment of the enol borinate with N-TSIM produced a single enol silyl ether, (E)-trimethyl (2-hepten-2-yloxy)silane (eq. 92), whose spectroscopic properties and GLC behaviour were identical to those reported earlier[9].

As mentioned previously, primary alkyl groups migrate preferentially over secondary alkyl groups in this reaction, and consequently the enol silyl ether resulting from sec-butyl transfer was not detected.

Besides being a convenient method of analysis, the exchange of the dibutylboryl by a trimethyl silyl group is also an excellent method for the preparation of regioisomerically and stereoisomerically pure enol silyl ethers. These compounds are usually obtained by enolization of the parent ketone followed by a tedious and laborious separation using preparative GLC methods[9].

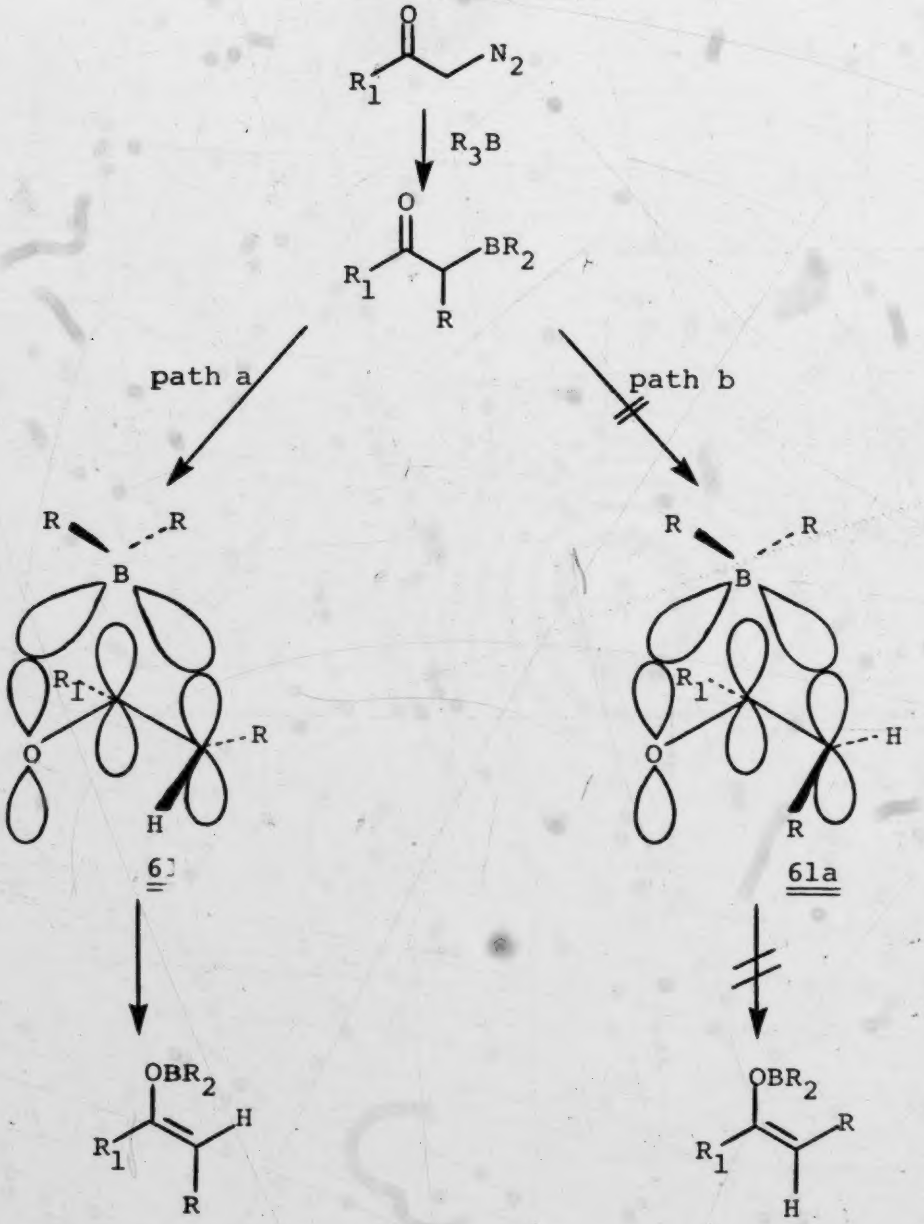
This reaction was also studied for 1-diazo-2-heptanone and tributylborane. ^1H and ^{13}C NMR spectroscopic data showed that only a single stereoisomer 60b had been formed, (eq. 93) (E)-dibutyl(5-undecen-6-yloxy)-borane, and the corresponding (Z)-isomer could not be detected.



60b (93)

The mechanistic interpretation of the stereoselective formation of the E-type enol borinate is only speculative at this moment. A possible mechanism is shown in Scheme XXIV. As discussed previously, the reaction is

Scheme XXIV

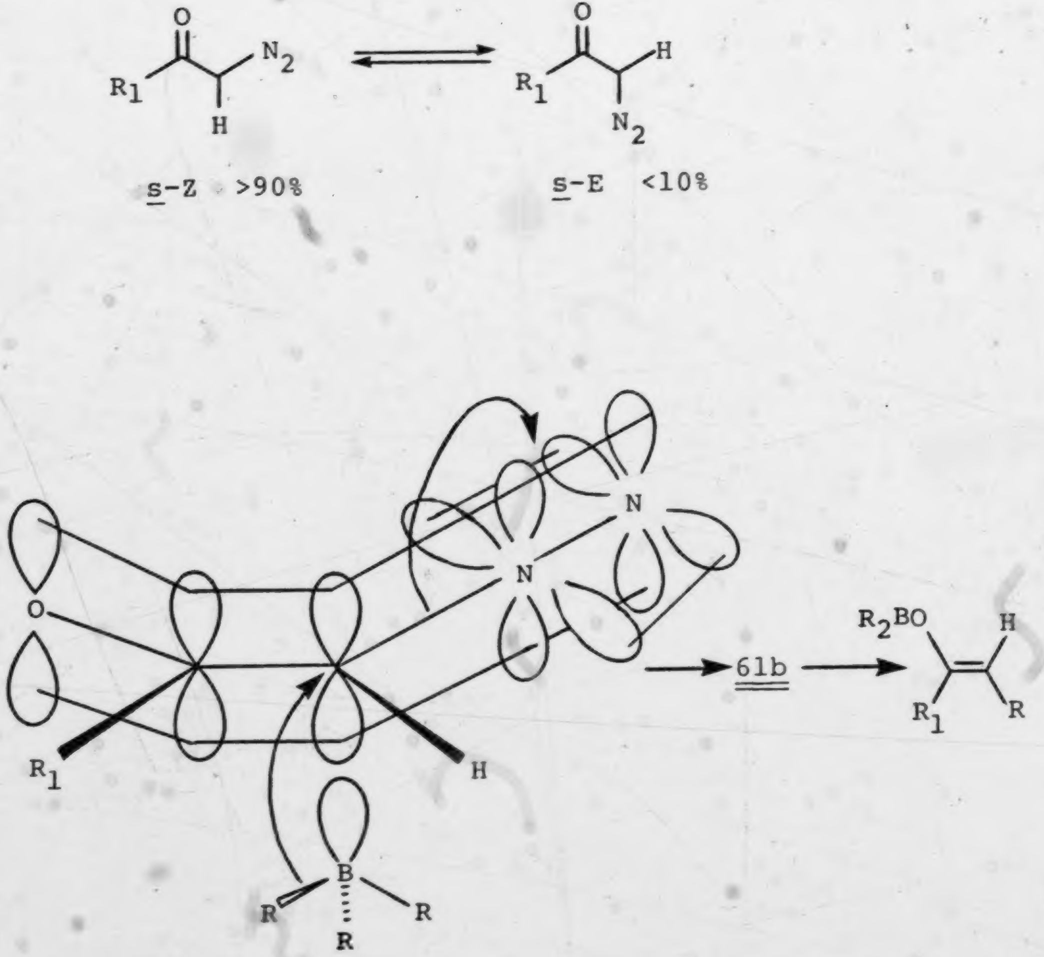

R3B
path a
path b
61
61a

believed to involve formation of an α-dialkylboryloxy ketone followed by tautomerization. This latter process may well go via a concerted pathway[174,175] since the boron atom has an orbital available for the formation of a new bond[174]. The structure of two such possible transition states are shown in 61a and 61b. It is feasible that transition state 61b is more stable than 61a due to the diminished steric interaction between the oxygen and hydrogen substituents in the former, whereas an oxygen-alkyl interaction is involved in the latter.

The stereoselective formation of enol borinates via this route may also be attributed to conformational control by the α-diazo ketone itself as shown in Scheme XXV. It has been reported that simple aliphatic α-diazo ketones exist mainly (>90%) as the s-Z conformer at ambient temperature whereas the s-E conformer is only present in minor amounts[177]. It is thus possible that the reaction mechanism follows a course involving:
(a) complexation of the organoborane to the s-Z conformer of the α-diazo ketone, followed by (b) internal "S_N2 type displacement" of nitrogen by the alkyl group, resulting in (c) transition state 61b, which gives rise to the E-isomer of the enol borinate.

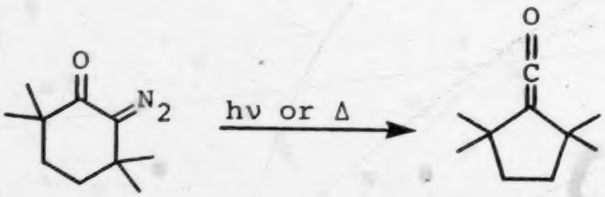
The literature provides some precedent for such a reaction mechanism[178], since it has recently been pointed out

Scheme XXV

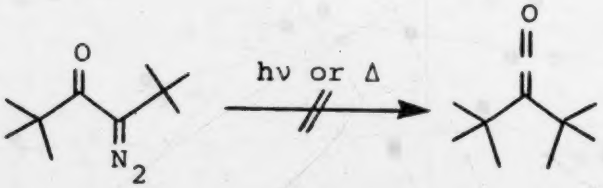

O
R1
N2
H
s-Z >90%
O
R1
H
N2
s-E <10%
O
N
N
R1
H
B
R
R
R
61b
R2BO
H
R1
R

that the Wolff rearrangement of α-diazo ketones (involving aprotic or photolytic formation of the intermediate ketene) proceeds preferentially from an s-Z conformation. The migrating group lies trans to the departing nitrogen moiety in such a conformation. For example 2-diazo-3,3,6,6-tetramethylcyclohexanone (s-Z) leads exclusively to the corresponding ketene (eq. 94) in this manner.

However, 4,-diazo-2,2,5,5-tetramethyl-3-hexanone which is predominantly present in the s-E conformation, does not result in any ketene formation (eq. 95).

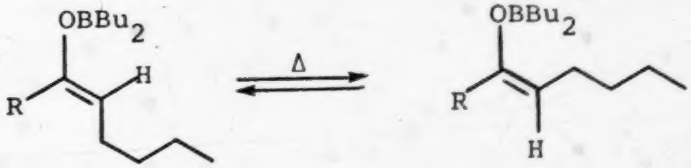


(94)



(95)

The isomerization of the E-type enol borinates to the thermodynamically more stable geometric Z-isomer was subsequently investigated (eq. 95). Enol borinate 59b (with a vinylic proton absorption at δ 4.52) was heated (24 hours at 100°C) in a sealed NMR tube and gradually a second vinylic proton absorption of 59a appeared at higher field (δ 4.39). (This provided complementary evidence that the original product was indeed the E-isomer[172]). Prolonged heating (ca. 40 hours at 140°C) of the sample eventually resulted in a mixture of stereoisomeric enol borinates with a constant composition of ca. 3:7 in favour of 59a (Z).



(96)

R = Me 59b 59a

R = C_5H_{11} 60b 60a

(E)-Dibutyl(5-undecen-6-yloxy)borane 60b was also equilibrated in this manner (eq. 96). Heating at 140°C for ca. 70 hours resulted in the complete conversion of 60b to its geometric Z-isomer (60a).

The mechanism of the enol borinate isomerization is merely speculative at the moment. It may involve transition states as shown in 61, but several other mechanisms have been considered for such an isomerization[65].

The problems associated with enolate chemistry have been accurately described by H.J. Reich and coworkers[179]: "The principal procedures for regiospecific preparation of enolates or silyl enol ethers are the dissolving metal reduction of enones and α-halo or α-acetoxy ketones. However, for these a non-specific (regioselective) introduction of unsaturation or halogen is frequently involved during preparation of the precursor."

The current method provides an excellent alternative since α-diazo ketones can be conveniently prepared from acid chlorides and diazomethane. The diazo substituent is thus specifically introduced which avoids the separation of regioisomeric mixtures of precursor. Significantly, this synthesis leads stereospecifically and regiospecifically to the thermodynamically less stable E-type enol borinates. The more stable Z-isomer can be obtained in high stereoisomeric purity by thermal equilibration. Moreover, simple exchange of the dialkylboryl group by a trimethylsilyl group results in the corresponding enol silyl ethers without loss of stereospecificity.

These obervations are very important for a variety of stereospecific syntheses, and potential synthetic applications are currently under active investigation in this laboratory.*

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* This reaction has already been applied by other workers[180].

CHAPTER VI

EXPERIMENTAL SECTION

General Considerations. Infrared (IR) spectra were recorded using a Unicam SP-1000 Infrared Spectrophotometer, Perkin-Elmer 421 Grating Spectrophotometer, or Nicolet 7199 FT-IR. The spectra are reported in reciprocal centimeters and the following abbreviations are used: s = strong, m = medium, w = weak and sh = shoulder.

Proton nuclear magnetic resonance (^1H NMR) spectra were run on a Varian A-60, Perkin-Elmer R-32 at 90 MHz, Varian HA-100 with a 12" Magnet, or Bruker WH-200 instrument. ^{13}C NMR spectra were recorded with a Bruker WP-60 or Bruker HFX-90 instrument. Chemical shifts are reported as δ values in parts per million downfield from tetramethylsilane. Coupling constants (J) are expressed in Hertz. Signal multiplicity is indicated as follows: s = singlet, d = doublet, t = triplet, q = quadruplet and m = multiplet. The numbering of hydrogen atoms is according to the carbon skeleton.

^{11}B NMR spectra were recorded on a Varian HA-100 15" Magnet instrument interfaced to a Digilab FTS/NMR-3 DATA system. The samples were dissolved in carbon tetrachloride or d_1-chloroform (in a 10 mm o.d. NMR tube), and spectra were measured using boron trifluoride etherate as an external standard (which was sealed in a capillary and positioned in the NMR tube). Absorptions downfield from $BF_3 \cdot OEt_2$ are prefixed with a minus sign, while absorptions upfield have a positive sign.

A good review on ^{11}B NMR spectroscopy, written by Lipscomb and Eaton[153], provided relevant comparison data for the present work.

Mass spectra were measured on an AEI Model MS-2 and Ms-12 spectrometer. Exact mass measurements were performed on an AEI Model MS-50 spectrometer. Mass spectra obtained with this spectrometer are simultaneously reported with the exact mass measurement. Thus, peaks with identical m/e but arising from different fragmentations are recorded as shown for example in Scheme XXXV. The most abundant fragments are reported with relative intensities as percent of the base peak intensity. The natural abundance of the isotopes of boron are: ^{10}B, 10.0129 (19.78%) and ^{11}B, 11.00931 (80.22%). The fragmentation patterns of 1,3-diketones are indicated in the text (Scheme XXXII to XXXVIII) and follow the trends which have been reported earlier for simple β-diketones[181,182].

Qualitative and quantitative analytical gas liquid chromatography (GLC) analyses were made on Varian Aerograph Series 1200 and 1400 instruments using an internal standard. Preparative GLC work was done on a Varian Aerograph A-90-P3 instrument.

Melting points are uncorrected and were taken on a

Reichert instrument.

The reactions involving boron compounds were carried out under an atmosphere of anhydrous and oxygen-free nitrogen. Commercial nitrogen (Union-Carbide) was purified either by passage through a sodium benzophenone ketyl solution in diglyme and a "drying train" (Drierite, conc. H_2SO_4, and Drierite) or by passage through a column of reduced BASF Catalyst R3-11 and a drying tower filled with Drierite.

In his most recent book, Organic Syntheses via Boranes, H.C. Brown[183] has included an excellent presentation on common bench-top laboratory techniques involving the handling of air- and water-sensitive substances. These simple techniques have been used in all reactions which required the exclusion of air and moisture.

Tetrahydrofuran (THF) was rigorously purified by pretreatment with Molecular Sieves, and then successively distilled from LAH and sodium benzophenone ketyl under nitrogen. Other solvents were dried and distilled from the appropriate reagent as summarized in the aforementioned book[183].

Reagents were purified according to established procedures[184]. Tributylborane (Callery), Triethylborane (Alfa Inorganics, Inc.) and borane-methyl sulfide complex (Aldrich Chemical Co., Alfa Products) were used without further purification.

In the syntheses of α-diazo ketones[185,186], diazomethane was prepared by the method of Moore and Reed[187], using the modification of Hooz and Bridson[185].

The Generation and Characterization of Dicyclohexyl(1-propenyl-2-oxy)borane. An oven-dried (12 h, 120°C) 50 mL flask equipped with a magnetic stirring bar, addition funnel, and septum inlet was flushed with dry, oxygen-free nitrogen, flame-dried, and then connected to an azotometer. The flask was cooled to 0°C and charged with cyclohexene (1.02 mL, 10 mmol) in THF (12 mL), after which borane-methyl sulfide complex (0.5 mL, 5 mmol) was slowly injected, while the temperature of the solution was kept at approximately 5°C (exothermic reaction). A white precipitate appeared within ca. 5 min and the mixture was stirred for 2 h at ice bath temperature. A solution of diazoacetone (0.42 gram, 5 mmol) in THF (10 mL) was gradually added and the temperature was kept at 5-7°C over a period of one h until the evolution of nitrogen ceased (~90%). The rubber septa were replaced by glass stoppers and the flask was evacuated (0.01 mm Hg) to remove THF over a period of 2 h, during which time the temperature did not exceed 10°C. Then d^8-toluene (3 mL) was added and the enol borinate solution was transferred under inert conditions to ^1H and ^{13}C NMR tubes, and sealed off under vacuum while cooled in liquid nitrogen. The NMR spectra were taken

at -10°C; ^{1}H NMR (d^{8}-toluene): δ 4.4 (s, 1H) vinylic protons, 1.9 (s) methyl, 2.1-1.1 (broad envelope) cyclohexyl groups (total 25H); ^{13}C-NMR (d^{8}-toluene): δ 22.1 ($\underline{\underline{C}}H_3$), 28 (cyclohexyl), 95.5 ($\underline{\underline{C}}H_2$=), 156.5 (O-$\underline{\underline{C}}$=).

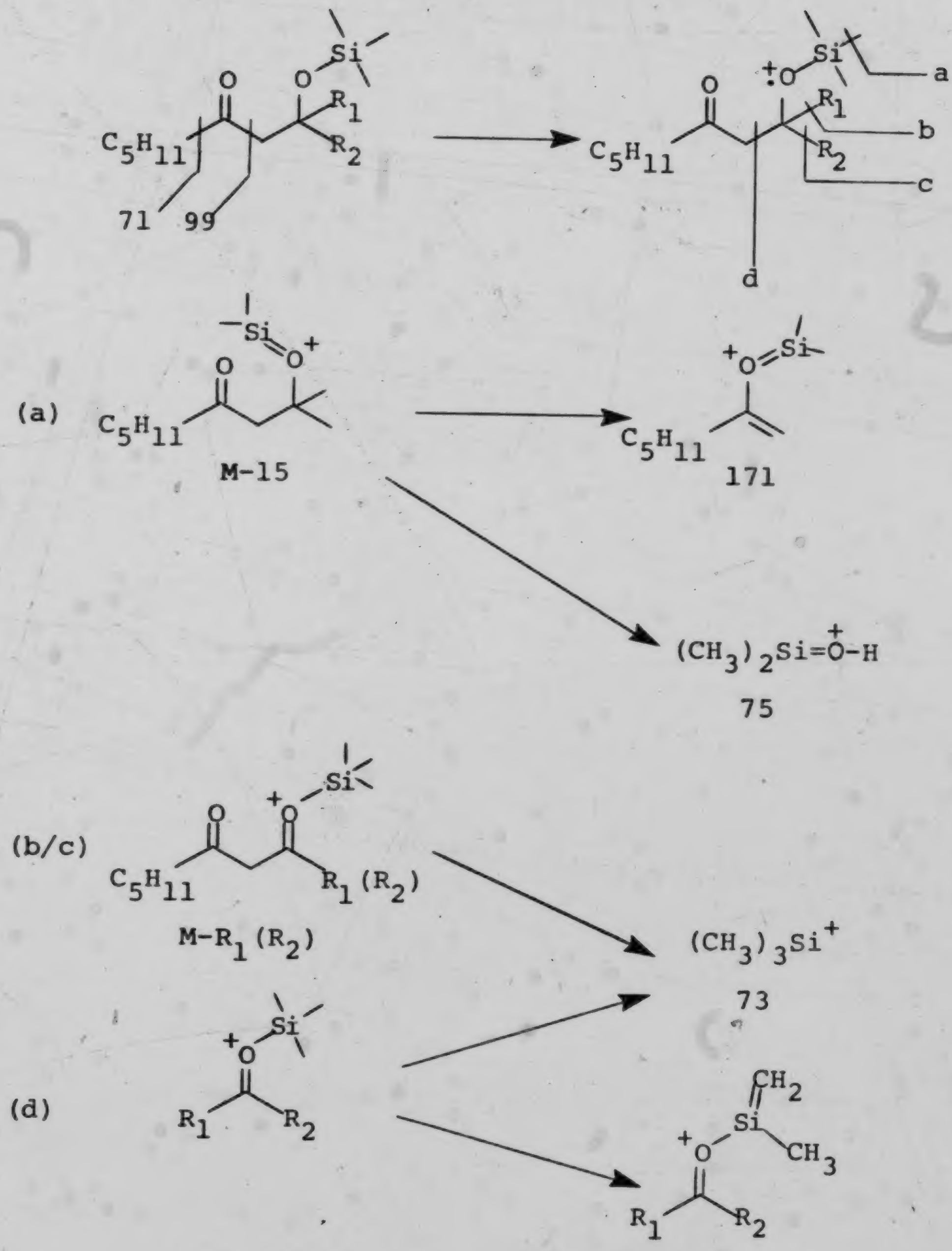
The methyl and vinylic protons in the ^{1}H NMR spectrum disappeared after the tube was kept at room temperature overnight, indicating the instability of this enol borinate.

Synthesis of 2-Methyl-2-trimethylsilyloxy-4-nonanone: A heterogeneous mixture of dicyclohexylborane (13 mmol) was prepared by hydroboration of cyclohexene (2.63 mL, 26 mmol) in anhydrous THF (15 mL). An azotometer was connected to the reaction flask and the mixture cooled to 5°C. The magnetically stirred mixture was maintained between 5 and 7°C, while a solution of 1-diazo-2-heptanone (1.40 g, 10 mmol) in THF (10 mL) was added dropwise over a period of 30 min. Stirring was continued for an additional h, after which the evolution of nitrogen (89%) had ceased. A solution of acetone (1.0 mL, 14 mmol) in THF (4 mL) was added at 5°C and the reaction mixture was stirred for 2 h at room temperature. N-trimethylsilylimidazole (2 mL, 14 mmol) was injected and the resulting mixture stirred for 1 h, after which time the THF was removed in vacuo. Distillation yielded 1.77 g (74%) of 2-methyl-2-trimethylsilyloxy-4-nonanone: bp 80°C (0.01 mm Hg); IR (neat): 1710 (C=O), 1250 (Si-Me), 1040 (Si-O-C), 840 cm^{-1} (Si-Me); ^{1}H NMR (CCl_4, $CHCl_3$): δ -0.22 (s, 9H) $Si{-}(C\underline{\underline{H}}_3)_3$, 0.56 (t, J = 7 Hz, 3H) C(9) protons, 0.98 (s, 6H) C(1) and C(10) protons superimposed on hydrocarbon moiety, 0.8-1.6 (m, 6H) C(6), C(7) and C(8) protons, 2.09 (t, J = 7 Hz, 2H) C(5) protons and 2.11 (s, 2H) C(3) protons; MS m/e: 244 (-) M$^+$, 229 (79) M$^+$-15, 171 (91), 131 (100), 115 (24), 99 (41), 75 (45), 73 (65) and 71 (14). The mass spectra of all β-trimethylsilyloxy ketones could be rationalized according to Scheme XXVI.

Mass measurement m/e, Calcd for $C_{12}H_{25}SiO_2$ (M$^+$-Me): 229.1623. Found: 229.1623.

Preparation of 2-Hydroxy-2-methyl-4-nonanone. A solution of the silylated derivative (360 mg, 1.5 mmol) in 20 mL of ethanol-water (3:1) was heated at 50°C for a few min in the presence of a trace of aq. HCl. The hydroxy ketone was extracted with hexane and the organic layer was dried over Na_2SO_4 and condensed in vacuo. Kugelrohr distillation afforded 2-hydroxy-2-methyl-4-nonanone (230 mg) as a colourless liquid in 92% yield; bp 80°C (0.01 mm Hg); IR (neat): 3450 (broad, OH), 1705 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$): δ 0.90 (t, J = 7 Hz, 3H) C(9) protons, 1.25 (s, 6H) C(1) and C(10) protons superimposed on hydrocarbon moiety, 1.0-1.8 (m, 6H) C(6), C(7) and C(8) protons, 2.43 (t, J = 7 Hz, 2H)

Scheme XXVI[a]


C5H11
71
99
a
b
c
d
(a)
M-15
171
(CH3)2Si=O+-H
75
(b/c)
M-R1(R2)
(CH3)3Si+
73
(d)
R1
R2
CH2
CH3

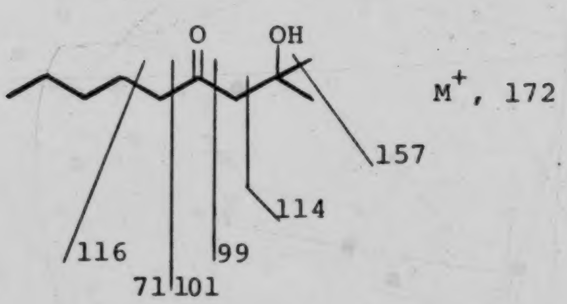
---

[a] The molecular ion peak of trimethylsilyl derivatives[142] is often not present, but the M-15 peak (cleavage of one Si-Me) is always present.

C(5) protons, 2.60 (s, 2H) C(3) protons; MS m/e: 172 (0.5) M^+, 157 (22) M^+-15, 154 (9), 116 (5), 114 (8), 101 (6), 99 (100) and 71 (39), which could be rationalized according to Scheme XXVII.

Mass measurement m/e, Calcd for $C_{10}H_{20}O_2$: 172.1487. Found: 172.1475.

Scheme XXVII



Synthesis of 3-Methyl-3-trimethylsilyloxy-5-decanone. This compound was prepared as described above from dicyclohexylborane (12 mmol), 1-diazo-2-heptanone (1.4 g, 10 mmol) and 2-butanone (1.3 ml, 15 mmol). Distillation afforded the product (1.85 g) in 72% yield as a colourless liquid: bp 80°C (0.01 mm Hg); IR (neat): 1710 (C=O), 1260 (Si-CH_3), 1040 (Si-O-C), 840 cm^{-1} (Si-CH_3); ^1H NMR (CCl_4, $CHCl_3$): δ -0.15 (s, 9H) Si-$\underline{\underline{H}}_3$, 0.5-0.8 (overlapping triplets, 6H) C(1) and C(10) protons, 1.03 (s, 3H) C(11) protons superimposed on hydrocarbon moiety, 0.8-1.5 (m, 8H) C(2), C(7), C(8) and C(9) protons, 2.0-2.4 (m, 4H) C(4) and C(6) protons. The multiplet arising from the C(4) and C(6) protons could be clarified by the addition of some C_6D_6: 2.03 (d, $J_{H_{AB}}$ = 13 Hz, 1H) C(4) H_A, 2.17 (d, $J_{H_{AB}}$ = 13 Hz, 1H) C(4) H_B, 2.06 (t, J = 7 Hz, 2H); MS m/e: 258 (-) M^+, 243 (19) M^+-15, 229 (75), 171 (33), 145 (44), 129 (17), 99 (100), 75 (74), 73 (60) and 71 (30).

Mass measurement m/e, Calcd for $C_{13}H_{27}SiO_2$ (M^+-Me): 243.1779. Found: 243.1772.

Synthesis of 2-Trimethylsilyloxy-4-nonanone. This was synthesized as described above from 1-diazo-2-heptanone (1.5 g, 11 mmol), dicyclohexylborane (13 mmol), and acetaldehyde (20 mmol). Microdistillation afforded a yellowish liquid (bp 75°C, 0.01 mm Hg) which was further purified by column chromatography over deactivated silica gel (with acetone) and hexane as an eluent to give 1.8 g of 2-trimethylsilyloxy-4-nonanone as a colourless liquid in 70% yield; GLC analysis (10% QF-1, 150°) showed the presence of a single isomer in 90% yield. IR (neat): 1710 (C=O), 1250 (CH_3-Si), 1040 (Si-O-C) 840 cm^{-1} (CH_3-Si); ^1H NMR (CCl_4, CH_2Cl_2): δ 0.03 (s, 9H) $C\underline{\underline{H}}_3$-Si, 0.87 (t, J = 7 Hz, 3H) C(9) protons, 1.10 (d, J = 6 Hz, 3H) C(1) protons, 0.9-1.8 (m, 6H) C(6), C(7) and C(8) protons, 2.1-2.6 (m, 4H) C(3) and C(5) protons, 4.0-4.1 (m, 1H) C(2) proton; MS m/e: 230 (1) M^+, 215 (100) M^+-15, 171 (99), 159 (43), 143 (14), 117 (77), 101 (15), 99 (28), 75 (86) and 73 (86).

Mass measurement m/e, Calcd for $C_{12}H_{26}SiO_2$: 230.1700. Found: 230.1681.

Synthesis of 1-Trimethylsilyloxy-3-octanone. A solution of dicyclohexyl(1-heptenyl-2-oxy)borane was prepared as described above from 1-diazo-2-heptanone (1.4 g, 10 mmol) and dicyclohexylborane (13 mmol). After the nitrogen evolution (93%) ceased, the reaction mixture was cooled to -78°C. Gaseous monomeric formaldehyde was introduced by pyrolysis (150°C) of paraformaldehyde. The heterogeneous mixture was stirred for one day at room temperature, after which time N-TSIM (2.0 mL, 13 mmol) was injected (exothermic reaction). The THF was evaporated and the remaining material was poured into pentane (100 mL). The flask was rinsed with pentane (50 mL) and the combined organic phase was filtered and concentrated to ca. 30 mL. The crude residue was resilylated with a few drops of N-TSIM, then washed with cold water (5 mL). The organic phase was dried over $MgSO_4$ and condensed under reduced pressure. Microdistillation afforded 1-trimethylsilyloxy-3-octanone in 33% yield: bp 70°C (0.02 mm Hg). GLC analysis (5% QF-1, 100°C) showed a single peak. IR (neat): 1710 cm^{-1} (C=O), 1240 (CH_3-Si), 1050 (Si-O-C), 840 cm^{-1}

(CH_3-Si); ^1H NMR (CCl_4, $CHCl_3$): δ 0.1 (s, 9H) $C\underline{\underline{H}}_3$-Si, 0.9 (t, J = 7 Hz, 3H) C(8) protons, 1.8-1.0 (m, 6H) C(5), C(6) and C(7) protons, 2.4 (t, J = 7 Hz, 2H) C(4) protons, 2.55 (t, J = 6 Hz, 2H) C(2) protons and 3.85 (t, J = 6 Hz, 2H); MS m/e: 216 (0.6) M^+, 215 (2), 201 (100) M^+-15, 171 (23), 160 (4), 145 (29), 131 (21), 103 (40), 99 (21), 75 (55) and 73 (45).

Mass measurement m/e, Calcd for $C_{11}H_{24}O_2Si$: 216.1545. Found: 216.1533.

Synthesis of 1-Cyclohexyl-1-trimethylsilyloxy-3-heptanone. This was prepared from 1-diazo-2-heptanone (1.4 g, 10 mmol) dicyclohexylborane (13 mmol), and cyclohexanecarboxaldehyde (13 mmol) as described previously. The crude material was purified by column chromatography over silica gel (acetone deactivated) using CH_2Cl_2-hexane (1:4) as eluent, and subsequent microdistillation to give 1-cyclohexyl-2-trimethylsilyloxy-4-nonane in 40% yield: bp 110°C (0.01 mm Hg). GLC analysis of the crude mixture showed a 60% yield (5% QF-1). IR (neat): 1715 (C=O), 1250 (Si-CH_3), 1040 (Si-O-C), 840 cm-1 (Si-CH_3); ^1H NMR (CCl_4, CH_2Cl_2): δ 0.05 (s, 9H) Si-$C\underline{\underline{H}}_3$, 0.8-1 (m, 20H) hydrocarbon fraction, 2.1-2.5 (m, 4H) and 3.9-4.2 (m, 1H); MS m/e: 298 (0.6) M^+, 283 (58) M^+-15, 227 (15), 215 (71), 185 (13), 171 (19), 152 (31), 137 (42), 99 (100), 75 (25), 73 (23) and 71 (21).

Synthesis of 1-Phenyl-1-octen-3-one. This was prepared as described above from 1-diazo-2-heptanone (1.40 g, 10 mmol), dicyclohexylborane (13 mmol) and benzaldehyde (13 mmol). Distillation (bp 90°C, 0.01 mm Hg) yielded a solid which was not the expected β-silyloxy ketone but the corresponding enone. The solid was recrystallized from pentane to give 1-phenyl-1-octen-3-one in 70% yield, which had identical spectroscopic data as reported in the literature[110]: mp 48°C (lit 47°C); IR (CCl_4): 1685, 1655, 1625 and 1610 cm^{-1}; ^1H NMR (CCl_4): 0.99 (m, 3H) C(8) protons 1.0-2.0 (m, 6H) C(5), C(6) and C(7) protons, 2.62 (t, J = 7 Hz, 2H) C(4) protons, 6.72 (d, J = 16 Hz, 1H) C(2) proton, 7.5 (d, J = 16 Hz) C(1) proton superimposed on aromatic protons and 7.1-7.7 (m, total 6H) phenyl + C(1) protons; MS m/e: 202 M^+, 146, 131, 103.

Isolation of (1-Imidazolyl)dicyclohexylborane. Approximately 2 g of the solid yellow residue obtained from the aldol condensation reactions was dissolved in 10 mL chloroform. Careful addition of acetone yielded a white precipitate. This material did not have a sharp melting point, but became less viscous above 200°C; IR (KBr pellet): 3160 (w), 2920 (s), 2850 (s), 2660 (w), 1700 (m), 1600 (m), 1525 (m, sh), 1510 (s), 1440 (s), 1080 (broad, s), 750 (s, sh) and 735 cm^{-1} (s); ^1H NMR ($CDCl_3$, CH_2Cl_2): δ 7.5 (broad, 1H), 6.8 (broad 2H) imidazole protons and

0.0-3.0 (m, 22H) cyclohexyl protons; MS m/e (70 eV, 250°C): 666 (1.2), 665 (3.1) $3M^+$-Im., 664 (1.9), 650 (0.2), 649 (0.8) $3M^+-C_6H_{11}$, 648 (0.5), 422 (0.6), 421 (2.4) $2M^+$-Im., 420 (1.1), 405 (0.3) $2M^+-C_6H_{11}$, 404 (0.1), 302 (0.2), 301 (0.1), 299 (0.4), 288 (0.7), 287 (3.3), 286 (1.5), 257 (2.2), 256 (1.0), 245 (0.8), 244 (3.3) M^+, 243 (1.9), 217 (1.7), 205 (4.3), 204 (2.1), 189 (1.2), 175 (2.6), 174 (1.6), 162 (18.2), 161 (100) $M^+-C_6H_{11}$, 160 (27.1), 159 (8.1), 119 (10.7), 95 (11.8), 83 (12.9), 82 (40.6), 81 (89.1), 80 (32.2), 79 (15.9), 69 (16.2), 68 (25.0), 67 (52.4), 55 (26.4), 54 (29.3), 53 (21.9), 52 (24.9), 41 (57.9).

Mass measurement m/e, Calcd for $C_{15}H_{25}N_2B$: 244.2111. Found: 244.2116.

Synthesis of (1-Imidazolyl)dicyclohexylborane from Chlorodicyclohexylborane. A heterogeneous mixture of dicyclohexylborane (30 mmol) was prepared in ether from cyclohexene (6.1 mL, 60 mmol) and the borane-methyl sulfide complex (3.0 mL, 30 mmol). This was reacted with dry HCl (30 mmol) in ether, and the evolution of hydrogen was quantitative. A second flask was charged with imidazole (30 mmol) and ether (30 mL), and cooled in an icebath after which a solution of methyllithium (30 mmol, 19 mL, 1.6 N) was gradually added (quantitative gas evolution). The chlorodicyclohexylborane was added to the second flask through a double-ended needle. The reaction mixture was stirred overnight at room temperature after which it was extracted with chloroform (250 mL). The organic layer was washed with two 100-mL portions of water, dried over $MgSO_4$, and condensed under reduced pressure to give 7 g of an off-white material. Precipitation from chloroform-acetone afforded a white solid, that showed identical properties with material isolated as described above. The molecular weight was ca. 1200 as determined by ebullioscopy (CH_2Br_2, 0.0076 M); the IR (KBr pellet) spectrum was identical to the previously isolated material; ^1H NMR ($CDCl_3$): δ 7.5 (m, 1H), 6.8 (m, 2H), 2.5-0.1 (m, 22H).

Mass measurement m/e (70 eV, 250°C), Calcd for $C_9H_{14}BN_2$ ($M^+-C_6H_{11}$): 161.1250. Found: 161.1250.

Synthesis of (1-Imidazolyl)dicyclohexylborane from Methyl Dicyclohexylborinate. This was prepared from methyl dicyclohexylborinate and N-trimethylsilylimidazole. A heterogeneous mixture of dicyclohexylborane (10 mmol) was prepared as described above, after which methanol (0.41 mL, 10 mmol) was added. Hydrogen evolved gradually in quantitative yield and the mixture was warmed to room temperature. N-TSIM (1.48 mL, 10 mmol) was added (slightly exothermic) and the solvent was evaporated after 30 min to give a bright white solid. This solid was evacuated (0.01 mm Hg) for 60 h. The NMR spectrum showed that some silyl ether was still present, which could be mostly removed at 100°C under vacuum. The molecular weight was ca. 3,000 as determined by ebullioscopic measurements (CH_2Br_2, 0.0073 M). The NMR and IR spectra were identical to the material isolated from the reaction of β-dicyclohexylboryloxy ketones and N-TSIM.

Mass measurement m/e, (70 eV, 280°C) Calcd. for $C_{15}H_{25}BN_2$: 244.2111. Found: 244.2107.

Deuterolysis experiments. An oven-dried 100 mL flask equipped with a magnetic stirring bar, addition funnel, Teflon stopcock and septum inlet was flushed with dry nitrogen, and charged with triethylborane (1.50 mL, 10.5 mmol) in THF (10 mL). A solution of diazoacetone (841 mg, 10.0 mmol) in THF (10 mL) was gradually added at 5-7°C and the reaction mixture was warmed to room temperature after the evolution of nitrogen ceased (quantitative). Then benzaldehyde (1.07 mL, 10.0 mmol) was added in 5 mL THF (exothermic).

A second oven-dried 200 mL flask, similarly equipped, was charged with diisopropylamine (2.1 mL, 15 mmol) in THF (20 mL). A solution of n-butyllithium (8.4 mL, 1.5 N, 12.5 mmol) in hexane was gradually added at -78°C. The β-diethylboryloxy ketone THF was then slowly added to the LDA solution at -78°C over a period of 1 h.

The resulting mixture was stirred for 0.5 h and approximately half of this solution was quenched with 37% DCl-D_2O (2 mL). The product was extracted with hexane (300 mL), and washed twice with water (50 mL). The organic layer was dried over $MgSO_4$ and condensed under vacuum to yield a yellow oil (1.1 g); IR (neat): 3440 (br), 1710 (s) and 1695 cm^{-1} (m, sh); ^1H NMR ($CDCl_3$, TMS): δ 7.4-7.1 (m, 5H) phenyl protons, 5.08 (d, J = 10 Hz, ~1/2H) *threo* $C\underline{\underline{H}}OH$, 4.71 (d, J = 9 Hz, ~1/2H) *erythro* $C\underline{\underline{H}}OH$, 3.1-2.6 (m, 1H) C(3) proton, 2.22 (s, ~1H) threo C(1) protons, 2.13 (s, ~1H) erythro C(1) protons, 1.8-0.7 (m) hydrocarbon moiety.

Synthesis of 1-Acetoxy-1-phenyl-4-[phenyl-acetoxymethyl]-hexan-3-one. An oven-dried (120°C, 12 h) 100 mL flask equipped with a magnetic stirring bar, addition funnel, septum inlet and Teflon stopcock was flushed with dry nitrogen, flame-dried, and then connected to an azotometer. The flask was cooled in an ice bath and charged with triethylborane (1.50 mL, 10.5 mmol) in THF (15 mL). To this solution was added, dropwise, (20 min) a solution of diazoacetone (0.840 g, 10.0 mmol) in THF (10 mL). The flask was allowed to rise to room temperature after nitrogen evolution ceased (quantitative), then benzaldehyde (1.01 mL, 10.0 mmol) was injected which resulted in an exothermic reaction (20° → 40°C).

A second oven-dried (120°C, 12 h) 200 mL flask equipped with a magnetic stirring bar, septum inlet and

Teflon stopcock was flushed with dry nitrogen, flame-dried, then charged with diisopropylamine (2.8 mL, 20 mmol) and THF (20 mL). The flask was cooled to -78°C, and a solution of n-butyllithium (8 mL, 1.5 N, 12 mmol) was gradually injected (5-10 min), while the temperature gradually rose to ca. -40°C. The β-diethylboryloxy ketone was then slowly added to the solution of lithium diisopropylamide at -78°C by a double-ended needle over a period of approximately 1 h, after which benzaldehyde (1.03 mL, 10 mmol) was injected. The Dry-Ice acetone bath was removed and the reaction mixture was warmed to -40°C. Acetic acid (1.0 mL, 17 mmol) was added at -78°C and the solution was warmed to room temperature. The reaction mixture was then oxidized with H_2O_2 (30%) in 3 N sodium acetate at 20°C (exothermic), and the product was extracted with ether (400 mL). The organic layer was successively washed with water (2 x 30 mL), 1.5 N aqueous HCl (50 mL), water (25 mL), 5% aqueous sodium bicarbonate (25 mL) and saturated aqueous sodium chloride (25 mL). The organic extract was dried over $MgSO_4$, and condensed to give a pale yellow oil (3.3 g): IR (neat): 3400 (broad), 1705 (s), 1605 (w), 1495 (w), 760 (s) and 700 cm^{-1} (s); ^1H NMR (CCl_4, TMS): δ 7.5-7.1 (m, 10H) phenyl protons, 5.3-4.5 (m, 2H) C$\underline{\underline{H}}$-OH, 4.2-3.1 (broad, 2H, exchangeable with D_2O) hydroxyl protons, 3.1-2.3 (m, 3H) C(2) and

C(4) protons, and 1.6-0.6 (m, 5H) C(5) and C(6) protons.

The dihydroxy ketone (1.5 g) was dissolved in pyridine (5 mL) and acetic anhydride (3 mL). A catalytic amount of 4-dimethylaminopyridine (ca. 10 mg) was added and the reaction mixture was stored overnight in a refrigerator (ca. 5°C). The product was extracted with a 2:1 (by volume) mixture of pentane and methylene chloride (300 mL), and the organic layer was consecutively washed with cold water (50 mL), 1.5 N aqueous HCl (50 mL), water 5% $NaHCO_3$ (25 mL), and water (25 mL). The extract was dried over $MgSO_4$ and condensed in vacuo to give 2.0 g of a yellow oil, which crystallized as a white material upon addition of ether (2 mL) and hexane (1 mL). The crystals (0.98 g) were washed twice with a small amount of hexane (mp 99-101°C). The mother liquor was chromatographed (Alumina, neutral, activity V 10% ether in hexane) to provide an additional 0.64 g of the diacetate. The overall yield was 84%, calculated from diazoacetone: mp 99-101°C; IR (CCl_4): 3100 (w), 3080 (w), 3040 (w), 1755 (s), 1725 (m), 1235 (s) and 700 cm^{-1} (m); ^1H NMR ($CDCl_3$, TMS): δ 7.6-7.2 (m, 10H) phenyl protons, 6.4-6.2 (m, 1H) C(1) proton, 5.79 (d, J = 10 Hz, ~1H) CH(Et)C$\underline{\underline{H}}$-OAc, 5.77 (d, J = 10 Hz, ~1H) HC(Et)C$\underline{\underline{H}}$OAc, 3.5-2.5 (m, 3H) C(2) and C(4) protons, 2.02 (s, 3H) 1-acetoxy protons, 1.96 (s, ~1.5H) $C\underline{\underline{H}}_3CO_2$CH-CH(Et), 1.80 (s, ~1.5H), $C\underline{\underline{H}}_3CO_2$CH-CH(Et), 1.75-0.9 (m, 2H) C(5) protons, 0.71 (t, J = 6 Hz) C(6) protons, and 0.61 (t, J = 7 Hz) C(6) protons (together 3H); MS m/e: 378 (-) M^+, 322 (2) M^+-HOAc, 280 (35), 279 (16), 262 (56) M^+-HOAC, 159 (15), 148 (6), 132 (92) and 131 (100).

Mass measurement (m/e), Calcd for $C_{21}H_{22}O_3$ (M^+-HOAc): 322.1569. Found: 322.1571.

Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 72.26; H, 6.85.

Synthesis of 4,8-Dihydroxy-5-ethyl-2-methyl-6-undecanone. This compound was prepared as described above from diazoacetone (0.841 g, 10.0 mmol), triethylborane (1.50 mL, 10.5 mmol), isovaleraldehyde (1.07 mL, 10.0 mmol), and butanal (1.0 mL, 11 mmol). After oxidation (H_2O_2, 3 N NaOAc) the crude dihydroxy ketone (2.55 g) was isolated as described before as a pale yellow oil: IR (neat): 3420 (broad), 1705 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS): 4.5-2.9 (m, 4H) CH-OH, 2H were exchangeable with D_2O, 2.9-2.2 (m, 3H) CH-CO-, 2.0-1.2 (m, 9H) C(2), C(3), C(9), C(10) and C(13) protons, 1.2-0.6 (m, 12H) methyl protons.

Synthesis of 4,8-Diacetoxy-5-ethyl-2-methyl-6-undecanone (34). The crude dihydroxy ketone (1.0 g) as prepared above was dissolved in pyridine (3 mL) and acetic anhydride (2 g). This resulted in an exothermic reaction upon addition of a catalytic amount of 4-dimethylaminopyridine. The mixture was stored overnight in a refrigerator (ca. 5°C), and worked up as described previously to give a yellow oil (1.64 g). The crude product was purified by column chromatography (neutral Alumina, activity V, 10% ether in hexane as eluent) to give 1.15 g of 4,8-diacetoxy-5-ethyl-2-methyl-6-undecanone as a pale oil in 91% overall yield from diazoacetone: IR (neat): 1740 (s), 1720 (sh), 1710 (sh) and 1240 cm^{-1} (s); ^1H NMR ($CDCl_3$, TMS): δ 5.5-5.0 (m, 2H) $C\underline{\underline{H}}OAc$, 3.0-2.3 (m, 3H) C(5) and C(7) protons, 2.02 (s), 1.98 (s) (6H, ~1:1 ratio) $C\underline{\underline{H}}_3CO_2$, 1.8-1.1 (m, 9H) C(2), C(3), C(9), C(10) and C(13) protons, 1.1-0.6 (m, 12H) methyl protons with doublet at 0.90 (J = 7 Hz) geminal dimethyl group; MS m/e: 328 (-) M^+, 268 (8.4) M^+-HOAc, 208 (12.4) M^+-2HOAC, 199 (14.1), 157 (70.1), 139 (61.1), 97 (100) and 69 (42.7).

Mass measurement m/e, Calcd for $C_{16}H_{28}O_3$ (M^+-HOAc): 268.2038. Found: 268.2037.

Synthesis of 5-Ethyl-2-methyl-4,7-undecadien-6-one. A small sample of the diacetate (ca. 100 mg) was impregnated on neutral Alumina (activity III) for 5 h and slowly eluted with hexane. Microdistillation afforded a colourless oil: bp 100°C (0.5 mm Hg); IR (neat): 1745 (w), 1665 (s), 1647 (w, sh), 1635 (w, sh), 1620 (s), 980 cm^{-1} (m); ^1H NMR ($CDCl_3$, TMS): δ 7.0-6.4

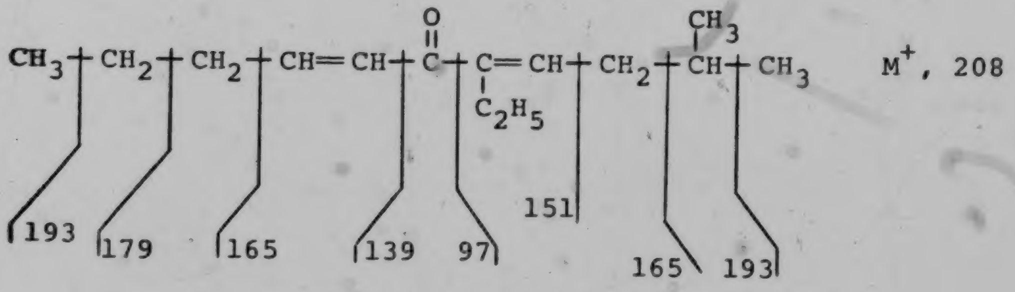
(m, 3H) vinylic protons, 2.5-2.0 (m, 6H) $C\underline{\underline{H}}_2$-C=C, 2.0-1.2 (m, 3H) C(2) and C(10) protons, 1.2-0.7 (m, 12H) methyl protons with doublet at 0.90 (J = 7 Hz) geminal methyl protons; MS m/e (100°C): 208 (12.7) M^+, 207 (14.0), 193 (4.9), 179 (3.4), 165 (100), 153 (6.2), 151 (10.8), 139 (32.7), 123 (46.9), 109 (46.4), 97 (29.1), 95 (17.6; 12.7), 91 (12.8), 81 (12.1), 69 (36.5), 67 (14.7), 57 (16.4), 55 (35.8; 46.7) and 53 (12.3).

Mass measurement m/e, Calcd for $C_{14}H_{24}O$: 208.1827. Found: 208.1832.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.69; H, 11.61.

The fragmentation pattern in the mass spectrum can be rationalized as depicted below (Scheme XXVIII). A number of fragments appear at intervals of 14 units, caused by the consecutive loss of methylene groups (208-193-179-165-151; 83-69-55; 123-109-95). The peak with m/e 123 ($C_8H_{11}O$) presumably arises by the loss

Scheme XXVIII



of C_2H_4 from fragment m/e 151 ($C_{10}H_{15}O$), which is then followed by the loss of methylene units (e.g. 109, C_7H_9O).

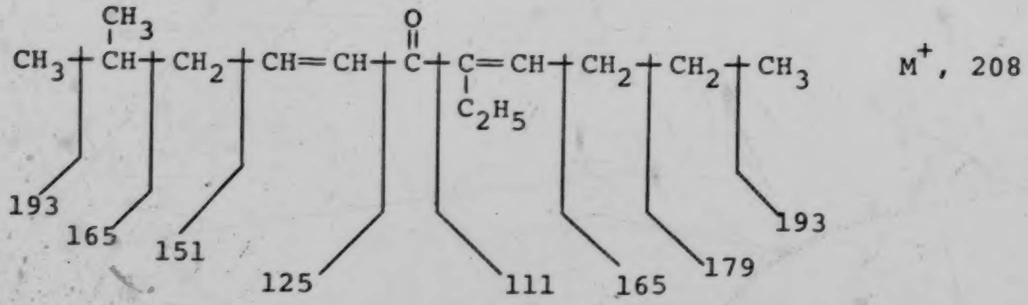
Synthesis of 4,8-Dihydroxy-7-ethyl-2-methyl-undecan-6-one. This was prepared as described above from diazoacetone (0.840 mg, 10.0 mmol), triethylborane (1.50 mL, 10.5 mmol), butanal (0.89 mL, 10.0 mmol) and isovaleraldehyde (1.20 mL, 11.0 mmol) to provide the crude product as a pale yellow oil (2.85 g): IR (neat): 3420 (broad), 1700 cm^{-1} (s); ^1H NMR ($CDCl_3$, TMS): δ 4.4-3.9 (m), 3.9-3.65 (m) $C\underline{\underline{H}}OH$ (together 2H), 3.6-3.0 (broad, 2H, D_2O exchangeable) $C\underline{\underline{H}}OH$, 2.7-2.1 (m, 3H) C(5) and (7) protons, 2.0-1.0 (m, 9H) C(2), C(3), C(9), C(10) and C(13) protons, 1.0-0.7 (m, 12H) methyl protons with a doublet at 0.90 ppm (J = 6 Hz) geminal dimethyl group.

Synthesis of 4,8-Diacetoxy-7-ethyl-2-methyl-undecan-6-one (35). The crude dihydroxy ketone (1.50 g) was dissolved in pyridine (5 mL) and acetic anhydride (2.0 g). A catalytic amount of 4-dimethylamino pyridine (ca. 10 mg) was added after which an exothermic reaction occurred. The reaction mixture was stored in the refrigerator (5°C) overnight; workup (as previously described) provided the crude diacetate (1.73 g). A portion of the pale yellowish oil (288 mg) was purified by column chromatography (neutral Alumina, activity V, 10% ether in hexane elution), to afford 0.247 g of a colorless liquid in 86% overall yield (calculated from diazoacetone) IR (neat): 1740 (s), 1715 (m, sh) and 1240 cm^{-1} (s); ^1H NMR ($CDCl_3$, TMS): δ 5.5-4.9 (m, 2H) $C\underline{\underline{H}}OAc$, 3.1-2.2 (m, 3H) C(5) and C(7) protons, 2.02, 2.01, 1.98 (3 s, 6H) $C\underline{\underline{H}}_3CO_2$, 1.8-1.1 (m, 9H) C(2), C(3), C(9), C(10) and C(13) protons, 1.1-0.7 (m, 12H); MS m/e: 268 (6.6) M^+-HOAc, 208 (15.6) M^+-2HOAC 185 (18.3), 171 (56.6), 154 (15.8), 125 (61.5) and 111 (100).

Mass measurement m/e, Calcd for $C_{16}H_{28}O_3$ (M^+-HOAc): 268.2038. Found: 268.2038.

Synthesis of 7-Ethyl-2-methyl-4,7-undecadien-6-one. This compound was prepared from the diacetoxy ketone (2.9 g) as previously described to give 2.0 g of a crude yellowish liquid. Microdistillation afforded the dienone as a colourless liquid: bp 63°C (0.01 mm Hg); IR (neat): 3040 (w), 1740 (w), 1720 (w), 1700 (m), 1665 (s), 1635 (m, sh), 1620 (s) and 980 cm^{-1} (m); ^1H NMR ($CDCl_3$, TMS): 7.0-5.4 (m, 3H) vinylic protons, 2.7-2.0 (m, 6H) $C\underline{\underline{H}}_2$-C=C, 1.9-1.2 ppm (m, 3H) C(2) and C(10) protons, 1.1-0.8 (m, 12H) methyl protons; MS m/e: 208 (19.3) M^+, 193 (3.0), 180 (3.6), 179 (6.4), 165 (21.0), 151 (100), 125 (31.3), 123 (17.8), 111 (11.7), 109 (15.5) and 55 (37.3; 20.0), which may be rationalized according to Scheme XXIX.

Scheme XXIX



Mass measurement m/e, Calcd for $C_{14}H_{24}O$: 208.1827. Found: 208.1831.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.24; H, 11.81.

Synthesis of 4,8-Dihydroxy-5-ethyl-2-methyl-9-undecen-6-one. This material was prepared as described previously from diazoacetone (841 mg, 10.0 mmol), triethylborane (1.50 mL, 10.5 mmol) isovaleraldehyde (1.07 mL, 10.0 mmol) and crotonaldehyde (1.07 mL, 13 mmol) to provide 2.79 g of the crude dihydroxy ketone as a yellowish oil: IR (neat): 3420 (broad), 1740 (s), 1705 (s), 1595 (w) and 975 cm^{-1} (m); ^1H NMR ($CDCl_3$, TMS): 6.0-5.3 (m, 2H) vinylic protons, 4.7-4.4 (m, 1H) C(8) proton, 4.1-3.8 (m, 1H) C(4) proton, 4.4-3.6 (broad, 2H), D_2O exchangeable) CH-O$\underline{\underline{H}}$, 3.0-2.1 (m, 3H), C(5) and C(7) protons, 2.0-1.1 (m, 8H) C(2), C(3), C(13) and C(11), as a doublet at 1.67 (J = 5 Hz), 1.1-0.7 (m, 9H), C(1), C(12) and C(14) methyl protons.

Synthesis of 4,8-Diacetoxy-5-ethyl-2-methyl-9-undecen-6-one (36). The crude dihydroxy ketone (1.0 g) was dissolved in pyridine (2 g) and acetic anhydride (2 g). An exothermic reaction occurred after addition of a catalytic amount of 4-dimethylaminopyridine (ca. 10 mg), and 1.49 g of a yellow oil was isolated after the usual workup procedure. The crude material was purified by column chromatography (neutral Alumina, activity V; 10% ether in hexane elution). This afforded the diacetate as a colourless oil in 93% overall yield (calculated from diazoacetone). IR (neat): 3040 (w), 1740 (s), 1720 (s, sh), 1710 (m, sh), 1640 (w), 1595 (w), 1240 (s), 1020 (m) and 965 cm^{-1} (m); ^1H NMR ($CDCl_3$, TMS): δ 6.3-5.9 (m, 4H), $C\underline{H}OAc$ and vinylic protons 3.0-2.3 (m, 3H) C(5) and C(7) protons, 2.02 (s, 3H) $C\underline{H}_3CO_2$-, 1.97 (s, 3H) $C\underline{H}_3CO_2$-, 1.66 (d, J = 7 Hz, 3H) C(11) protons, 1.8-1.1 (m, 5H) C(2), C(3) and C(13) protons, 1.1-0.7 (m, 9H) C(1), C(12) and C(13) protons with a doublet a 0.88 (J = 6 Hz) for the geminal dimethyl group; MS m/e: 267 (3.0), 266 (5.3) M^+-HOAc, 251 (1.3), 224 (4.9), 223 (5.4), 207 (5.8), 206 (13.9) M^+-2HOAc, 199 (28.1), 139 (100), 126 (10.9), 113 (47.7), 111 (18.9; 14.0), 95 (54.7), 84 (14.4), 71 (27.3) and 69 (42.9).

Mass measurement m/e, Calcd for $C_{16}H_{26}O_3$ (M^+-HOAc): 266.1882. Found: 266.1885.

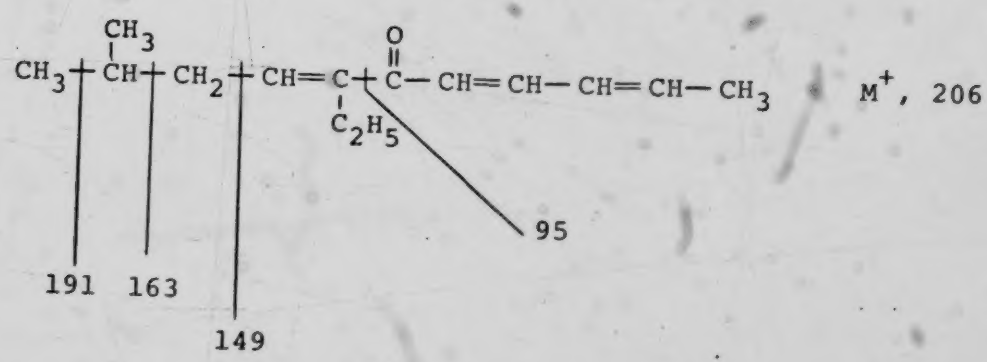
Synthesis of 5-Ethyl-2-methyl-4,7,9-undecatrien-6-one. The diacetate (ca. 2 g) was impregnated on an Alumina column (neutral, activity II) and the resulting trienone was eluted with hexane. Distillation afforded a yellow liquid (1.4 g): bp 90°C (0.03 mm Hg); IR (neat): 3030 (w), 1740 (w), 1660 (s), 1630 (s), 1590 (s) and 1000 cm^{-1} (s); ^1H NMR ($CDCl_3$, TMS): δ 7.4-5.8 (m, 5H) vinylic protons, 2.38 (q, J = 7 Hz, 2H) C(13) protons, 2.16 (t, J = 7 Hz, 2H) C(3) protons, 1.84 ("d", J = 5 Hz, 3H) C(11) protons, 1.8-1.4 (m, 1H) C(2) proton, 0.96 (t, J = 7 Hz, 3H; d, J = 6 Hz, 6H) C(1), C(12) and C(14) protons; MS m/e: 206 (56.1) M^+, 191 (42.7), 163 (70.0), 150 (18.2), 149 (42.3), 123 (18.4), 121 (19.3), 107 (26.0), 95 (100), 93 (10.4), 91 (32.6), 79 (37.7) and 77 (32.1).

Mass measurement m/e, Calcd for $C_{14}H_{22}O$: 206.1671. Found: 206.1676.

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.51; H, 10.91.

The fragmentation pattern of the mass spectrum is rationalized as depicted in Scheme XXX, but a number of peaks arise obviously from more complex rearrangements. Many fragments appear at intervals of 14 units, due to the loss of methylene fragments (206-191; 149-135-121; 93-79; 91-77).

Scheme XXX



Synthesis of 4,8-Dihydroxy-7-ethyl-2-methyl-9-undecen-6-one. This compound was prepared as previously described from diazoacetone (1.68 g, 20.0 mmol), triethylborane (3.0 mL, 21 mmol) crotonaldehyde (1.67 mL, 20.0 mmol) and isovaleraldehyde (2.6 mL, 24 mmol) to give a pale yellow oil (5.3 g): IR (neat): 3420 (m), 1705 (s), 1660 (w), 1635 (w) and 970 cm^{-1} (m); ^1H NMR ($CDCl_3$, TMS): δ 7.1-5.1 (m, 2H) vinylic protons, 4.1-3.9 (m, 2H) CHOH, 3.3-2.9 (broad, 2H, D_2O exchangeable) CHOH, 2.9-2.1 (m, 3H) C(5) and C(7) protons, 2.0-1.1 (m, 8H) C(2), C(3), C(13) and C(11) protons, as a doublet at 1.70 (J = 7 Hz), 1.1-0.7 (m, 9H) C(1), C(12) and C(14) protons with a doublet at 0.90 (J = 6 Hz).

Synthesis of 4,8-Diacetoxy-7-ethyl-2-methyl-9-undecen-6-one (37). The crude dihydroxy ketone was dissolved in pyridine (5 g) and acetic anhydride (5 g). Addition of a catalytic amount of 4-dimethylaminopyridine (ca. 10 mg) induced an exothermic reaction, and the mixture was stored in a refrigerator (ca. 5°C) overnight. The usual workup procedure afforded 5.5 g of a yellowish oil, which could be purified by column chromatography (neutral Alumina, activity V; 10% ether in hexane elution). The diacetate was isolated as a colourless oil in 84% overall yield, (from diazoacetone): bp 120°C (0.05 mm Hg); IR (neat): 3040 (w), 1740 (s), 1720 (s, sh), 1665 (m), 1640 (m), 1240 (s), 1020 (m) and 970 cm^{-1} (m); ^{1}H NMR ($CDCl_3$, TMS): δ 7.2-5.6 (m, 2H) vinylic protons, 5.5-5.0 (m, 2H) $C\underline{\underline{H}}OAc$, 3.1-2.2 (m, 3H) C(5) and C(7) protons, 2.02, 1.97, 1.92 (3 singlets, 6H) $C\underline{\underline{H}}_3CO_2$-, 2.8-1.1 (m, 8H) C(2), C(3), C(13) and C(11) protons, as a doublet at 1.70 (J = 7 Hz), 1.1-0.7 (m, 9H) C(1), C(12) and C(14) protons; MS m/e: 266 (3.9) M^+-HOAc, 223 (3.5), 207 (5.5), 206 (21.7) M^+-2HOAc, 191 (19.0), 163 (6.5), 154 (27.4), 149 (9.8), 139 (9.2), 123 (43.3), 122 (12.0), 111 (79.3), 97 (17.9), 96 (100), 81 (35.3) and 71 (31.8).

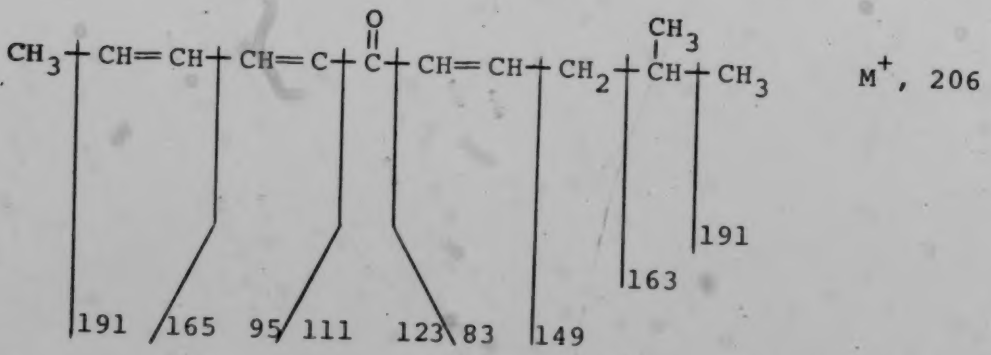
Mass measurement (m/e), Calcd for $C_{16}H_{26}O_3$ (M^+-HOAc): 266.1882. Found: 266.1885.

Synthesis of 7-Ethyl-2-methyl-4,7,9-undecatrien-6-one. The aforementioned diacetate (4.1 g) was impregnated on Alumina (activity V, neutral) and slowly eluted with Skelly B. This process was repeated with Alumina (activity III), followed by microdistillation to give the trienone (2 g) as a yellow liquid: bp 100°C (0.05 mm Hg); IR (neat): 3040 (w), 1745 (w), 1690 (w, sh), 1660 (s), 1640 (s), 1615 (s), 980 (m) and 970 cm^{-1} (m); ^1H NMR ($CDCl_3$, TMS): δ 7.1-5.1 (m, 5H) vinylic protons, 2.43 (q, J = 7 Hz, 2H) C(13) protons, 2.10 ("t", J = 6 Hz, 2H), 1.87 (d, J = 6 Hz, 3H) C(11) protons, 1.9-1.5 (m, 1H) C(2) proton, 0.98 (t, J = 7 Hz, 3H) and 0.95 (d, J = 7 Hz, 6H) C(1) and C(2) geminal methyl protons; MS m/e (100°C): 207 (19.8), 206 (67.4) M^+, 191 (88.6), 165 (27.3), 163 (39.8), 150 (20.1), 149 (100), 135 (29.5), 123 (56.8), 121 (14.7), 111 (38.0), 109 (17.1), 96 (17.1), 95 (27.2), 93 (19.2), 91 (14.8), 83 (15.8), 81 (13.8), 79 (21.4), 77 (16.3), 69 (17.1; 11.0), 67 (18.7), 55 (39.4; 48.8), and 53 (12.4).

Mass measurement m/e, Calcd for $C_{14}H_{22}O$ (M^+): 206.1670. Found: 206.1674.

The fragmentation pattern of the mass spectrum can be rationalized as depicted in Scheme XXXI, although

Scheme XXXI



$$CH_3-CH=CH-CH=C-\overset{O}{\overset{\|}{C}}-CH=CH-CH_2-\overset{CH_3}{\overset{|}{C}H}-CH_3$$

some peaks must arise from more complex rearrangements. Many fragments appear at intervals of 14 units, due to the loss of methylene fragments (206-191; 163-149-135-121; 123-109; 95-81-67-53; 83-69-55), which is typical for hydrocarbons.

Attempted Proton Abstraction of 5-[1-Dibutylboryloxy-1-phenylmethyl]-6-undecanone with Lithium *tert*-Butoxide. An oven-dried 100 mL flask equipped with a magnetic stirring bar, addition funnel, septum inlet and Teflon stopcock was flushed with dry, oxygen-free nitrogen, flame-dried and charged with tributylborane (1.83 mL, 7.6 mmol) in THF (10 mL). A solution of 1-diazo-2-heptanone (1.04 g, 7.4 mmol) in THF (10 mL) was gradually added at 5-7°C. The resulting solution (almost colourless) was warmed to room temperature after nitrogen evolution ceased (quantitative), and benzaldehyde (0.75 mL, 7.4 mmol) was injected (exothermic).

A second 200 mL flask, similarly equipped, was flushed with nitrogen, flame-dried, and charged with *tert*-butyl alcohol (1.5 mL, 2 equiv., 16 mmol) in THF (10 mL). A solution of n-butyllithium (4.6 mL, 7.4 mmol) in hexane was slowly added at -78°C and the flask was gradually warmed to (0°C/20 min). The solution of lithium *tert*-butoxide was slowly added to the β-dibutylboryloxy ketone solution at -78°C after which the reaction mixture was allowed to warm to 5°C over a period of 3 h. An aliquot (ca. 5 mL) was quenched with 37% DCl-D_2O (1 mL), then oxidized with hydrogen peroxide (30%) in aqueous sodium acetate (3 N) and extracted with ether. The organic layer was washed with water, aqueous sodium bicarbonate, dried over $MgSO_4$, and condensed, to give the α-benzhydryloxy substituted 6-undecanone as a yellow oil (ca. 0.4 g): IR (neat): 3450 (broad), 1710 cm^{-1} (s); ^1H NMR (CCl_4, TMS): δ 7.5-6.9 (m, 5H) phenyl protons, 4.8-4.4 (m, 1H) CHOH, 3.8-3.2 (broad, 1H) OH proton, 2.9-2.5 (m, 1H) C(5) proton, 2.5-2.1 (m, 2H) C(7) protons, 1.9-0.6 (m, 18H) hydrocarbon moiety. This spectrum is identical with the spectrum of the aldol product prepared directly via hydrolysis of the β-boryloxyketone 38.

The remainder of the reaction mixture was warmed to room temperature (over 2 h) and worked up as described above to provide material with the following properties IR (neat): 3400 (broad), 1705 (s), and 1660 cm^{-1} (m). The latter absorption indicated that β-elimination had taken place.

Proton Abstraction of 5-[1-Dibutylboryloxy-1-phenylmethyl]-6-undecanone with Potassium tert-Butoxide. A solution of this aldol condensation product (5.2 mmol) was prepared (as described before) from 1-diazo-2-heptanone (0.73 g, 5.2 mmol) tributylborane (1.3 mL, 5.5 mmol) and benzaldehyde (0.52 mL, 5.2 mmol) in approximately 30 mL THF. This was added to a suspension of freshly sublimed potassium tert-butoxide (0.63 g, 5.6 mmol) in 10 mL THF at -30°C. An aliquot (ca. 5 mL) was quenched with 37% DCl-D_2O (2 mL) after reaction for 1.5 h at -30°C. The crude β-hydroxy ketone was isolated as previously described, after oxidation with 30% hydrogen peroxide in aqueous 3 N sodium acetate, to give a yellow oil (ca. 200 mg); IR (neat): 3400 (broad) and 1710 cm^{-1} (s); ^1H NMR (CCl_4, TMS): δ 7.5-6.9 (m, 5H) phenyl, 4.8-4.4 (m, 1H) C$\underline{\underline{H}}$OH, 3.0-2.6 (m, 1H) C(5) proton, 2.6-2.2 (m, 1H) C(7) proton, 2.0-0.7 (m, 18H) hydrocarbon moiety. Thus, one proton at C(7) was replaced by deuterium.

The remainder of the reaction mixture was warmed to room temperature and the product arising from β-elimination became more pronounced as shown by the appearance of a peak at 1660 cm^{-1} in the infrared spectrum.

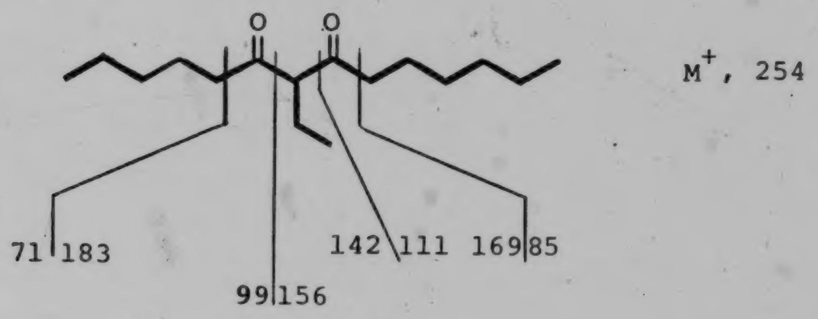
Synthesis of 2,2,5-Triethyl-6-hexyl-4-pentyl-1H-boroxazine. An oven-dried 100 mL flask, equipped with a magnetic stirring bar, addition funnel, and septum inlet was flushed with anhydrous, oxygen-free nitrogen, and charged with triethylborane (1.69 mL, 12 mmol) and THF (10 mL). The flask was cooled in an ice-bath and connected to an azotometer. A solution of 1-diazo-2-heptanone (1.4 g, 10 mmol) in THF (10 mL) was gradually added, while the temperature was kept at 5-7°C. After the nitrogen evolution ceased (quantitative), heptanenitrile (2.06 mL, 15 mmol) was injected and the mixture stirred overnight at room temperature. Then aqueous 0.1 N HCl (ca. 20 mL) was added (in an attempt to hydrolyze the product), followed by addition of pentane (50 mL). The organic layer was washed with water, dried over $MgSO_4$ and condensed under atmospheric pressure to give a yellow oil (3 g). Microdistillation afforded a mixture of heptanenitrile and 4-nonanone (bp 50°C, 0.01 mm Hg) as shown by GLC-mass spectrometry (10% DEGS, 8' x 1/8", 150°C); 4-nonanone, m/e: 142 (8.2) M^+, 100 (4.6), 99 (40.0), 86 (19.8), 71 (82.0), 58 (38.5), 55 (13.6), 43 (100), 41 (34.5) and 29 (22.7); heptanenitrile (m/e): 112 (0.6), 111 (0.3) M^+, 110 (4.2), 96 (10.7), 83 (65.3), 82 (80.6), 81 (10.8), 69 (10.6), 68 (17.0), 57 (10.0), 56 (9.3), 55 (46.4), 54 (50.9), 43 (60.4), 42 (20.2), 41 (100), 40 (12.3), 39 (45.2) and 29 (43.1); IR (neat, mixture of nitrile and ketone): 2240 (m) and 1710 cm^{-1} (s). The yellow residue was purified by column chromatography (silica gel, 20% CH_2Cl_2 in Skelly B) to give the boroxazine (1.05 g) as a bright yellow oil in 35% overall yield; IR (neat): 3390 (m), 3340 (w, sh), 1610 (s), and 1495 cm^{-1} (s); ^1H NMR (CCl_4, C_6H_6): δ 0.1-0.5 (q, J = 6 Hz, 4H) $C\underline{\underline{H}}_2$-B, 0.5-1.0 (m, 15H) $C\underline{\underline{H}}_3$, 1.0-1.8 (m, 14H) β, γ, δ and ε C$\underline{\underline{H}}_2$ of the pentyl and hexyl substituents, 2.0-2.5 (m, 6H) C$\underline{\underline{H}}_2$ adjacent to C(4), C(5) and C(6) of the boroxazine ring, 5.7 (broad, 1H) N$\underline{\underline{H}}$, exchangeable with NaOD; ^{11}B NMR (CCl_4): δ -6 (broad ^{11}B); MS m/e (70 eV, 100°C): 293 (16.44), 292 (100) and 291 (24.98).

Mass measurement m/e, Calcd for $C_{18}H_{35}NO^{11}B$ (M^+-ethyl): 292.2812. Found: 292.2815.

Synthesis of 7-Ethyltetradecane-6,8-dione. A sample of 2,2,5-triethyl-6-hexyl-4-pentyl-1H-boroxazine (0.230 g) was dissolved in 70% aqueous acetic acid (13 mL) and the mixture was heated on a steam bath (1 h) until the yellow colour disappeared. Skelly B (25 mL) was added and the organic layer was washed with water, 5% aqueous sodium bicarbonate, dried over $MgSO_4$ and condensed in vacuo. Microdistillation afforded the dione as a colourless liquid (ca. 150 mg) in approximately quantitative yield: bp 120°C (0.01 mm Hg); IR (neat): 1725 (s), and 1720 cm^{-1} (s); ^{1}H NMR ($CDCl_3$, TMS): δ 0.7-1.9 (m, 9H) C$\underline{\underline{H}}_3$, 1.1-2.0 (m, 16H) hydrocarbon moiety, 2.45 (t, J = 7 Hz, 4H) C(5) and C(9) C$\underline{\underline{H}}_2$ adjacent to the carbonyl groups, 3.57 (t, J = 7.5 Hz, 1H) C(7) C$\underline{\underline{H}}$; MS m/e (70 eV, 50°C): 254 (14.70) M^+, 184 (4.31), 183 (11.80), 169 (12.00), 156 (20.35), 142 (39.62), 114 (11.70), 113 (98.75), 100 (13.96), 99 (100), 86 (61.64), 85 (26.28), 71 (40.21; 10.93), 58 (14.00), 57 (13.84) and 55 (13.93; 15.63), which could be rationalized as shown in Scheme XXXII.

Mass measurement m/e, Calcd for $C_{16}H_{30}O_2$: 254.2245. Found: 254.2244.

Scheme XXXII



Synthesis of 2,2,5-Triethyl-6-methyl-4-pentyl-1H-boroxazine. An oven-dried 100 mL flask equipped with a magnetic stirring bar, addition funnel, and septum inlet was flushed with dry nitrogen and then connected to an azotometer. The flask was cooled to 0°C and charged with triethylborane (0.77 mL, 5.5 mmol) in THF (10 mL). A solution of 1-diazo-2-heptanone (0.70 g, 10 mmol) in THF (10 mL) was gradually added at 5-7°C, and nitrogen evolved in quantitative yield over a period of 20 min. Then acetonitrile (0.53 mL, 10 mmol) was injected and the nearly colourless solution turned yellow after about 15 min. The mixture was warmed to 50°C and left overnight at this temperature. After cooling to room temperature, the mixture was extracted wtih pentane (300 mL), and the organic layer was washed with three 50-mL portions of water, then dried over $MgSO_4$ and condensed in vacuo. The yellow residue was purified by column chromatography (silica gel, 20% CH_2Cl_2 in Skelly B) to give the boroxazine as a bright yellow oil (1.09 g) in 87% yield (calculated from diazo ketone); IR (neat): 3390 (m), 3330 (sh), 1615 cm^{-1} (s); ^1H NMR (CCl_4, TMS): δ 0.23 (t, J = 6.5 Hz, 4H) B-$C\underline{\underline{H}}_2$, 0.5-1.1 (m, 12H) all methyl protons except 6-methyl protons, 1.1-1.8 (m, 6H) β, γ and δ $C\underline{\underline{H}}_2$ of the 4-pentyl group, 1.9-2.5 (m, 7H) $C\underline{\underline{H}}_3$ and $C\underline{\underline{H}}_2$ protons adjacent to C(4), C(5) and C(6) of the boroxazine ring, 5.9 (broad, 1H); ^{11}B NMR (CCl_4): δ -6 (broad, ^{11}B); MS m/e (70 eV, 100°C): 223 (11.36), 222 (100) and 221 (25.52).

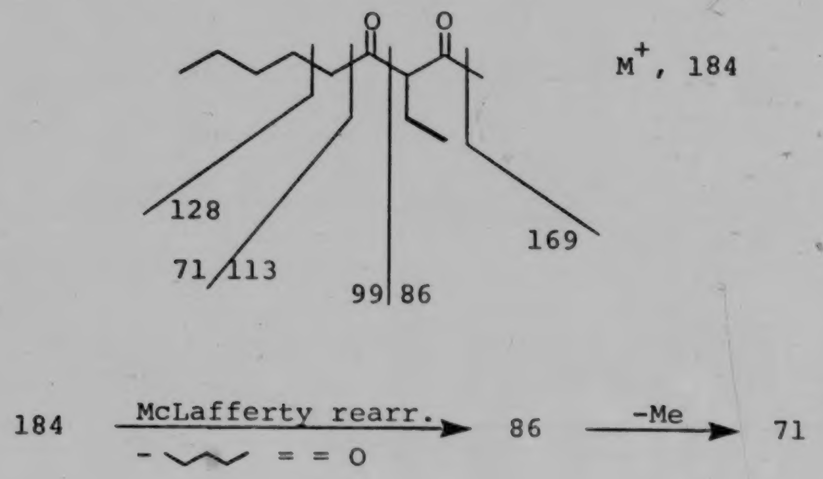
Mass measurement m/e, Calcd for $C_{13}H_{25}NO\ ^{11}B$ (M^+-Et): 222.2029. Found: 222.2031.

Synthesis of 3-Ethylnonane-2,4-dione. 2,2,5-Triethyl-6-methyl-4-pentyl-1H-boroxazine (371.1 mg, 1.48 mmol) was dissolved in a 4:1 mixture of ethanol-water (10 mL) after which 3 drops of conc. HCl (1-2 equivalent) was added. The solution was refluxed until it turned colourless (~ 2 h). The reaction mixture was extracted with CH_2Cl_2 (40 mL) and the organic phase was washed with water, dried over $MgSO_4$, and condensed in vacuo. Column chromatography (20% CH_2Cl_2

in hexane) of the residue yielded 3-ethylnonane-2,4-dione (262 mg) as a colourless liquid (96% yield); IR (neat): 1725 (s), 1700 cm^{-1} (s); ^1H NMR ($CDCl_3$, TMS): δ 0.88 (t, J = 7 Hz, 6H) C(9) and C(11) protons, 1.1-1.9 (m, 8H) C(6), C(7), C(8) and C(10) protons, 2.15 (s, 3H) C(1) methyl protons, 2.47 (t, J = 7 Hz, 2H) C(5) $C\underline{\underline{H}}_2$, 3.55 (t, J = 7 Hz, 1H) C(3) $C\underline{\underline{H}}$; MS m/e (70 eV, 25°C): 184 (17.5) M^+, 169 (2.8), 128 (6.0), 125 (4.9), 113 (32.5), 100 (8.1; 4.3), 99 (100), 86 (39.0), 85 (5.3), 71 (62.2; 28.6), 58 (11.2), and 55 (15.0; 14.4), rationalized according to Scheme XXXIII.

Mass measurement m/e, Calcd for $C_{11}H_{20}O_2$: 184.1459. Found: 184.1463.

Scheme XXXIII



Synthesis of 2,2,5-Tricyclopentyl-6-methyl-4-pentyl-1H-boroxazine. An oven-dried 100 mL flask, equipped with a magnetic stirring bar, thermometer, addition funnel, reflux condenser, and septum inlet was flushed with nitrogen and charged with cyclopentene (1.50 mL, 17 mmol) in THF (14 mL). The flask was cooled (ice-bath) and borane-methyl sulfide complex (0.55 mL, 5.5 mmol) was slowly injected. The cooling bath was removed and the reaction mixture was stirred for 3 h at room temperature. Then a solution of 1-diazo-2-heptanone (0.70 g, 5 mmol) in THF (10 mL) was gradually added at 5-7°C, after which acetonitrile (0.53 mL, 10 mmol) was injected, and the reaction mixture was refluxed for 14 h. The flask was cooled to room temperature and the mixture extracted with pentane (300 mL). The organic phase was washed several times with water, dried over $MgSO_4$ and condensed in vacuo to give a brown residue. Column chromatography (silica gel, 20% CH_2Cl_2 in Skelly B) afforded the desired boroxazine (0.72 g) as a bright yellow oil in 39% yield, which crystallized upon refrigeration: mp ~5-10°C; IR (neat): 3390 (w), 3340 (w), 1705 (m), and 1605 cm^{-1} (s); ^1H NMR ($CDCl_3$, C_6H_6): δ 0.5-1.0 (m, 5H) $C\underline{\underline{H}}$-B and $C\underline{\underline{H}}_3$ of the 4-pentyl substituent, 1.0-1.9 (m, 30H) hydrocarbon moiety, 1.93 (s), 1.9-2.5 (m) (together 6H) $C\underline{\underline{H}}_3$ and $C\underline{\underline{H}}_2$ adjacent to C(4) and C(5) $C\underline{\underline{H}}$ of the boroxazine ring, 5.9 (broad, 1H) $N\underline{\underline{H}}$; ^{11}B NMR (CCl_4): δ -6 (broad, ^{11}B); MS m/e (70 eV, 150°C): 303 (22.09), 302 (100) and 301

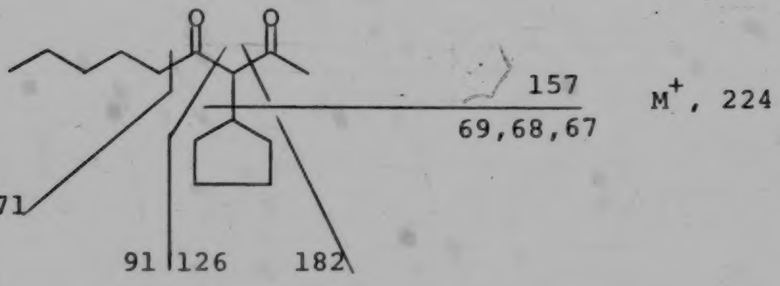
(30.99).

Mass measurement m/e, Calcd for $C_{19}H_{33}NO^{11}B$ (M^+-cyclopentyl): 302.2655. Found 302.2650.

Synthesis of 3-Cyclopentylnonane-2,4-dione. 2,2,5-Tricyclopentyl-6-methyl-4-pentyl-1H-boroxazine (585 mg, 1.57 mmol) was dissolved in 70% aqueous ethanol (14 mL) and 6 drops of conc. HCl were added (~3 equiv). The solution was refluxed until it turned colourless (ca. 5 h). The reaction mixture was extracted with CH_2Cl_2 and the organic layer was washed with water, dried over $MgSO_4$ and condensed in vacuo to give a yellowish oil. Microdistillation afforded the dione as a colourless liquid in 89% yield: bp 70°C (0.01 mm Hg). Spectral data indicated the presence of an enol-keto mixture: IR ($CHCl_3$): 3200-3000 (broad, sh), 1725 (sh), and 1695 cm^{-1} (s); ^1H NMR (CCl_4, TMS): δ 0.88 (t, J = 7 Hz, 3H) C(9) $C\underline{\underline{H}}_3$, 1.0-1.4 (m, 6H) C(6), C(7) and C(8) $C\underline{\underline{H}}_2$, 1.4-2.0 (m, 9H) cyclopentyl protons, 2.03 (s), 2.0-2.6 (m) (together 5H) C(1) and C(5) protons, 3.25 (d, J = 11 Hz, 0.5H) C(3) $C\underline{\underline{H}}$, and 4.5 (broad, 0.5H) $O\underline{\underline{H}}$, exchangeable with EtOD; MS m/e (70 eV, 25°C): 224 (2.84) M^+, 182 (4.69), 157 (35.17), 129 (10.49), 126 (100), 114 (4.42), 111 (21.09), 108 (12.53), 100 (12.31), 99 (72.58), 97 (13.35), 83 (14.68), 71 (47.34), 69 (19.76), 68 (11.02), 67 (25.26), 59 (27.92), 58 (17.27), 57 (15.36), 55 (19.35), which could be rationalized. as shown in Scheme XXXIV.

Mass measurement m/e, Calcd for $C_{14}H_{24}O_2$: 224.1776. Found: 224.1779.

Scheme XXXIV



$157 - CH_3CO \longrightarrow 114$

$126 - Me \longrightarrow 111$

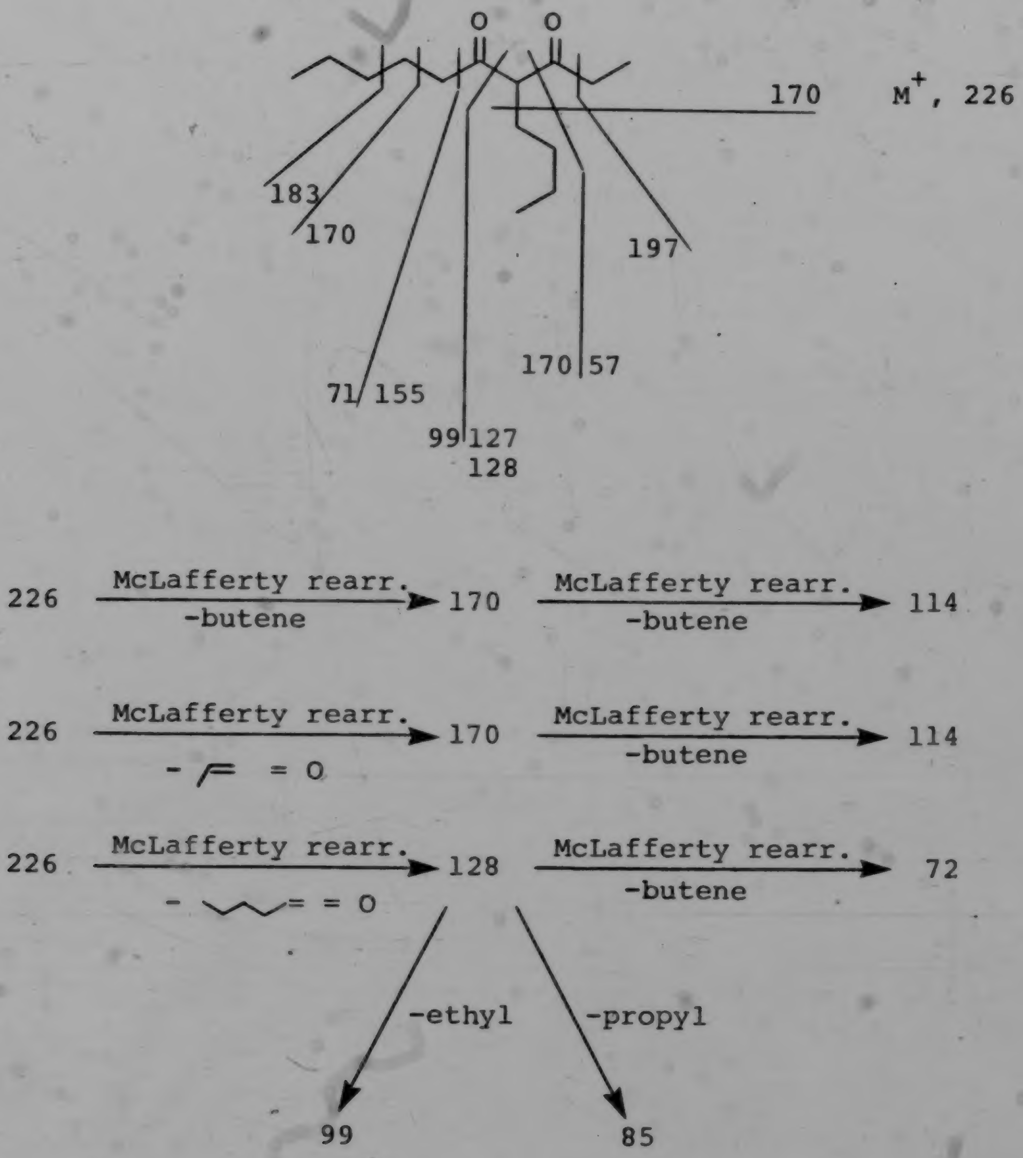
Synthesis of 2,2,5-Tributyl-6-ethyl-4-pentyl-1H-boroxazine. This was prepared as described above from 1-diazo-2-heptanone (1.40 g, 10 mmol), tributylborane (2.88 mL, 12 mmol) and propanenitrile (1.06 mL, 15 mmol). The nitrogen evolution was 95% and the reaction mixture was refluxed for 5 h. The typical yellow colour became quite apparent within 1 h. Column chromatography (silica gel, 20% CH_2Cl_2 in Skelly B) afforded the boroxazine (2.64 g) as a bright yellow oil in 76% yield; IR (neat): 3400 (m), 3340 (w), 1710 (w), 1615 (s), and 1495 cm^{-1} (s); ^1H NMR ($CDCl_3$, $CHCl_3$): δ 0.1-0.5 (m, 4H) $C\underline{\underline{H}}_2$-B, 0.7-1.8 (m, 33H) hydrocarbon moiety, 2.0-2.5 (m, 6H) $C\underline{\underline{H}}_2$ adjacent to C(4), C(5) and C(6) of the boroxazine ring, 6.1 (broad, 1H) $N\underline{\underline{H}}$; ^{11}B NMR ($CDCl_3$): δ -3 (broad, ^{11}B); MS m/e (70 eV, 50°C): 293 (19.34), 292 (100) and 291 (24.70).

Mass measurement m/e, Calcd for $C_{18}H_{35}NO\ ^{11}B$ (M^+-Bu): 292.2812. Found: 292.2808.

Synthesis of 4-Butyl-decane-3,5-dione. 2,2,5-Tributyl-6-ethyl-4-pentyl-1H-boroxazine (0.810 g, 2.32 mmol) was dissolved in 80% aqueous ethanol (20 mL) and 0.6 mL of conc. HCl (~2 equiv.) was added. The mixture was refluxed for 4 h and processed as previously described. Column chromatography (silica gel, Skelly B: CH_2Cl_2: methanol = 84:15:1) afforded the dione as a colourless oil (0.482 g) in 93% yield; IR (neat): 1725 (s), and 1700 cm^{-1} (s); ^1H NMR ($CDCl_3$, TMS): δ 0.86 (t, J = 7 Hz, 6H), C(10) and C(14) $C\underline{\underline{H}}_3$, 1.01 (t, J = 7 Hz, 3H) C(1) $C\underline{\underline{H}}_3$, 1.0-2.0 (m, 12H) hydrocarbon moiety, 2.42 (t, J = 7 Hz), 2.0-2.6 (m) (together 4H) C(2) and C(6) $C\underline{\underline{H}}_2$, 3.62 (t, J = 7 Hz, 1H) C(4) $C\underline{\underline{H}}$; MS m/e (70 eV, 50°C): 226 (18.18), 197 (9.73), 183 (8.77), 170 (6.60, 10.67), 155 (10.72), 128 (41.19), 127 (13.81), 114 (10.84, 18.91), 99 (100), 85 (22.96), 72 (18.63), 71 (33.15), 57 (53.33) and 55 (13.16), which could be rationalized according to Scheme XXXV.

Mass measurement m/e, Calcd for $C_{14}H_{26}O_2$: 226.1932. Found: 226.1927.

Scheme XXXV


O
O
170
M⁺, 226
183
170
197
71
155
170
57
99
127
128
226
McLafferty rearr.
-butene
170
McLafferty rearr.
-butene
114
226
McLafferty rearr.
= O
170
McLafferty rearr.
-butene
114
226
McLafferty rearr.
= = O
128
McLafferty rearr.
-butene
72
-ethyl
-propyl
99
85

Synthesis of 2,2,5-Tributyl-4-cyclohexyl-6-methyl-1H-boroxazine. This was synthesized as described above from 1-cyclohexyl-2-diazo-1-ethanone (0.69 g, 5 mmol), tributylborane (1.32 mL, 5.5 mmol), and acetonitrile (0.53 mL, 10 mmol). The solution was stirred overnight at 45°C, and subsequent column chromatography of the reaction mixture (silica gel, 20% CH_2Cl_2 in Skelly B) provided the boroxazine as a bright yellow oil (1.19 g) in 70% yield; IR (neat): 3395 (w), 3340 (sh), 1700 (w), 1610 (s), and 1495 cm^{-1} (s); ^1H NMR ($CDCl_3$, $CHCl_3$): δ 0.0-0.4 (m, 4H) $C\underline{\underline{H}}_2$-B, 0.6-1.0 (m, 9H) methyl protons, 1.0-1.8 (m, 22H) hydrocarbon moiety, 1.9 (s), 1.8-2.5 (m) (together 6H) protons at the α-carbon atoms adjacent to C(4), C(5) and C(6) of the boroxazine ring; ^{11}B NMR (CCl_4): δ -6 (broad, ^{11}B); MS m/e (70 eV, 150°C): 291 (20.28), 290 (100) and 289 (25.73).

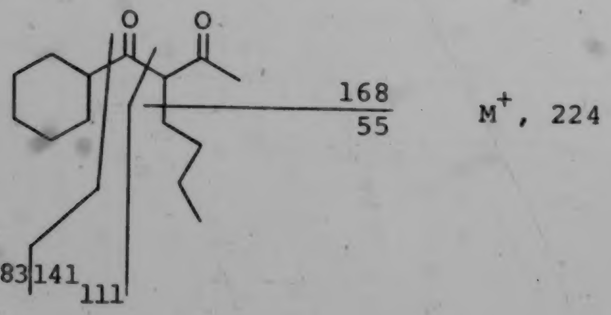
Mass measurement m/e, Calcd for $C_{18}H_{33}NO^{11}B$ (M^+-Bu): 290.2659. Found: 290.2657.

Synthesis of 3-Butyl-1-cyclohexylbutane-1,3-dione. 2,2,5-Tributyl-4-cyclohexyl-6-methyl-1H-boroxazine (0.470 g, 1.35 mmol) was dissolved in 70% aqueous ethanol (14 mL) and conc. HCl (6 drops, ~2 equiv.). The yellow solution was refluxed until it turned colourless (4 h) and then worked up as previously described.

Microdistillation afforded the dione (0.285 g) as a colourless liquid in 95% yield: bp 70°C (0.01 mm Hg); IR (neat): 1725 (s) and 1695 cm^{-1} (s); ^{1}H NMR ($CDCl_3$, TMS): δ 0.7-1.0 (t, J = 7 Hz, 3H) $C\underline{\underline{H}}_3$ of $n-C_4H_9$, 1.0-2.0 (m, 16H) hydrocarbon moiety, 2.1 (s, 3H) C(4) $C\underline{\underline{H}}_3$, 2.2-2.6 (m, 1H) cyclohexyl $C\underline{\underline{H}}$, and 3.77 (t, J = 7 Hz, 1H); MS m/e (70 eV, 25°C): 224 (6.76) M^+, 168 (6.07), 141 (7.38), 111 (34.27), 83 (100), 71 (10.84) and 55 (21.29), which could be rationalized according to Scheme XXXVI.

Mass measurement m/e, Calcd for $C_{14}H_{24}O_2$: 224.1776. Found: 224.1778.

Scheme XXXVI



Synthesis of 2,2,5-Tributyl-4-isopropyl-1H-boroxazine. This was prepared as described above from 1-diazo-3-methyl-2-butanone (0.56 g, 5.0 mmol), tributylborane (1.32 mL, 5.5 mmol) and acetonitrile (0.53 mL, 10 mmol). The nitrogen evolution was quantitative and the solution was heated overnight at 40°C. Column chromatography (silica gel, 20% CH_2Cl_2 in Skelly B) afforded the boroxazine (1.20 g) as a bright yellow oil in 78% yield; IR (neat): 3390 (w), 3340 (w), 1705 (w), 1610 (s) and 1500 cm^{-1} (s); ^1H-NMR ($CDCl_3$, C_6H_6): δ 0.0-0.3 (m, 4H) $C\underline{\underline{H}}_2$-B, 1.02 (d, J = 6.5 Hz) $CH(C\underline{\underline{H}}_3)_2$, and 0.6-1.6 (m) (together 27H) hydrocarbon moiety, 1.98 (s), 1.9-2.3 (m) (together 5H) $C\underline{\underline{H}}_3$ and $C\underline{\underline{H}}_2$ adjacent to C(5) and C(6) of the boroxazine ring, 2.72 (septet, J = 6.5 Hz, 1H) $-C\underline{\underline{H}}(CH_3)_2$, and 5.8 (broad, 1H) $N\underline{\underline{H}}$; ^{11}B NMR (CCl_4): δ -6 (broad, ^{11}B); MS m/e (70 eV, 100°C): 291 (20.28), 290 (100) and 289 (25.73).

Mass measurement m/e, Calcd for $C_{15}H_{29}NO^{11}B$ (M^+-Bu): 250.2346. Found: 250.2344.

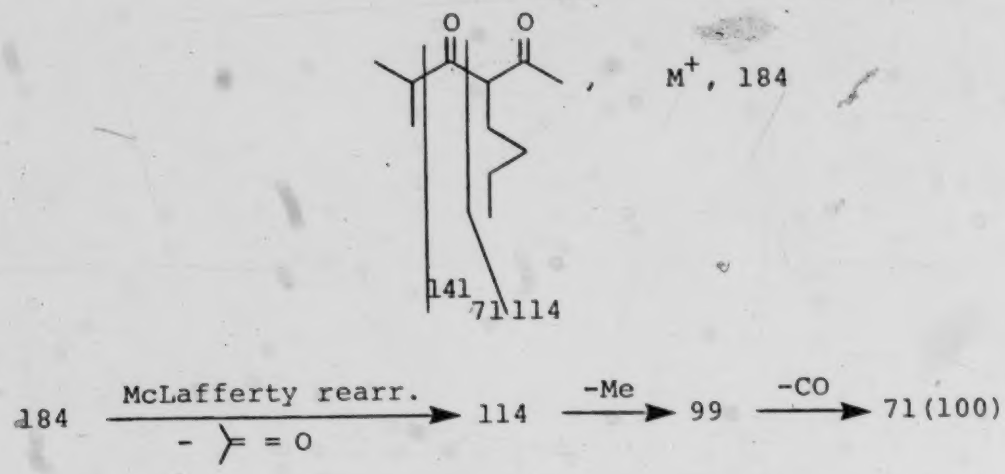
Synthesis of 3-Butyl-5-methylhexane-2,4-dione.

2,2,5-Tributyl-4-isopropyl-6-methyl-1H-boroxazine (0.493 g, 1.60 mmol) was dissolved in 70% aqueous ethanol (13 mL) and 5 drops of conc. HCl (ca. 1.5 equiv) were added. The mixture was refluxed for 4 h and the product was extracted with Skelly B (50 mL). Microdistillation afforded the dione (0.280 g) as a colourless liquid in 94% yield: bp 60°C (0.01 mm Hg); IR (neat): 1725 (s) and 1700 cm^{-1} (s); ^1H NMR ($CDCl_3$, TMS): δ 0.98 (d, J = 7 Hz) $-CH(C\underline{\underline{H}}_3)_2$, 0.7-1.9 (m) (together 15H) hydrocarbon moiety 1.97 (s, 3H) C(1) $C\underline{\underline{H}}_3$, 2.60 (septet, J = 7 Hz, 1H) $-C\underline{\underline{H}}(CH_3)_2$, and 3.55 (t, J = 7 Hz, 1H) C(3) $C\underline{\underline{H}}$; MS m/e (70 eV, 25°C): 184

(10.62) M^+, 141 (14.54), 128 (12.52), 114 (6.59), 99 (23.01), 85 (4.04; 6.73), 71 (6.73; 100), 56 (23.34) and 55 (11.17), which could be rationalized as shown in Scheme XXXVII.

Mass measurement m/e, Calcd for $C_{11}H_{20}O_2$: 184.1463. Found: 184.1462.

Scheme XXXVII



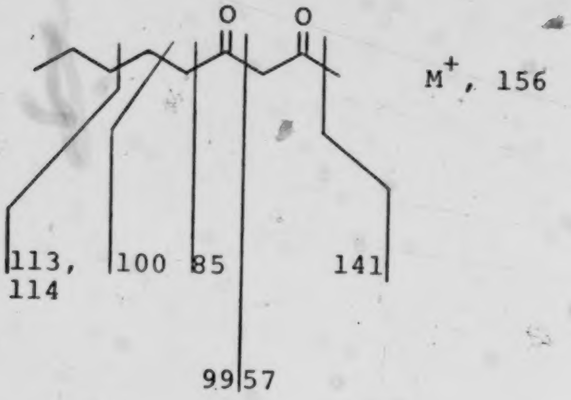
Synthesis of 2,2-Dicyclohexyl-6-methyl-4-pentyl-1H-boroxazine. An oven-dried 100 mL flask, equipped with a magnetic stirring bar, thermometer, reflux condenser, addition funnel and septum inlet was thoroughly flushed with oxygen-free, anhydrous nitrogen and connected to an azotometer. The flask was cooled in an ice-bath and charged with cyclohexene (1.21 mL, 12 mmol) and THF (10 mL). Borane-methyl sulfide complex (0.6 mL, 6 mmol) was slowly injected and the mixture was stirred for 2.5 h. To the suspension of dicyclohexylborane was slowly added a solution of 1-diazo-2-heptanone (0.70 g, 5 mmol) over a period of 15 min. The solution was stirred for 1 h at 5-7°C until a quantitative yield of nitrogen had evolved, after which acetonitrile (0.53 mL, 10 mmol) was added. The solution was stirred overnight at room temperature and then heated to 40°C for 1 h. The reaction mixture was extracted with pentane (200 mL) and the organic phase was washed with two 50-mL portions of water, then dried over $MgSO_4$ and condensed in vacuo to give a dark brown syrup (1.9 g). The residue was purified by column chromatography (silica gel, 20% CH_2Cl_2 in Skelly B) to give a bright yellow oil (1.2 g) in 73% yield; IR (neat): 3395 (m), 1625 (s), and 1540 cm^{-1} (s); ^1H NMR ($CDCl_3$, C_6H_6): δ 0.0-0.5 (m, 2H) C$\underline{\underline{H}}$-B, 0.5-1.7 (m, 29H) C$\underline{\underline{H}}_2$ of cyclohexyl groups and β, γ and δ C$\underline{\underline{H}}_2$ of the 4-pentyl substituent, 1.77 (s) 6-methyl protons, 1.7-2.1 (m) (together 5H) C$\underline{\underline{H}}_2$ adjacent to the C(4) of the boroxazine ring, 4.53 (broad singlet, 1H) C(5) proton and 5.6 (broad, 1H) N$\underline{\underline{H}}$; ^{11}B NMR (CCl_4): δ -6 (broad, ^{11}B); MS m/e (70 eV, 100°C): 249 (16.92), 248 (100) and 247 (25.55).

Mass measurement m/e, Calcd for $C_{15}H_{27}NO^{11}B$ (M^+-C_6H_{11}): 248.2185. Found: 248.2191.

Synthesis of Nonane-2,4-dione. 2,2-Dicyclohexyl-6-methyl-4-pentyl-1H-boroxazine (0.978 g, 2.95 mmol) was dissolved in 80% aqueous ethanol (20 mL) and conc. HCl (0.6 mL, ~1.5 equiv.) was added. The solution was refluxed until it turned colourless (3 h), and the product was extracted with CH_2Cl_2 (80 mL). The organic layer was washed with water, dried over anhydrous magnesium sulfate and condensed. Column chromatography (silica gel, 20% CH_2Cl_2 in Skelly B) afforded nonane-2,4-dione (0.428 g, 2.75 mmol) as a colourless liquid in 93% yield; IR (neat): 1730 (w), 1705 (w) and 1605 cm^{-1} (broad, strong); ^1H NMR ($CDCl_3$, TMS): δ 0.88 (t, J = 6 Hz, 3H) C(9) $C\underline{\underline{H}}_3$; 1.1-1.8 (m, 6H) C(6), C(7) and C(8) $C\underline{\underline{H}}_2$, 2.02 (s, 2.6H) C(1) $C\underline{\underline{H}}_3$ in the enol-ketone form, 2.1-2.6 (m, 2.4H) C(5) $C\underline{\underline{H}}_2$ and C(1) $C\underline{\underline{H}}_3$ in the diketone form, 3.54 (s, 0.3H), C(3) $C\underline{\underline{H}}_2$ in the diketone form, 5.47 (s, 0.85H) C(3) in the enol-ketone form, and 15.5 (broad, 0.85H) enol proton, detected at -40°C; MS m/e (70 eV, 50°C): 156 (11.18) M^+, 141 (7.40), 114 (10.86), 113 (14.05), 100 (14.63; 50.32), 99 (8.88), 86 (5.03), 85 (100), 83 (30.41), 82 (39.54), 67 (13.37), 57 (30.01) and 55 (18.30), which could be rationalized according to Scheme XXXVIII.

Mass measurement m/e, Calcd for $C_9H_{16}O_2$: 165.1150. Found: 156.1150.

Scheme XXXVIII



Attempted Methylation of Dicyclohexyl(1-hepten-2-yloxy)borane with Trimethylsulfonium[188], Trimethylsulfoxonium[189] or N-Methylpyridinium[190] Iodide. An oven-dried 100 mL flask, equipped with a magnetic stirring bar, addition funnel, thermometer and septum inlet was flushed with nitrogen and cooled in an ice-bath. The flask was charged with borane-methyl sulfide complex (1.3 mL, 13 mmol) and THF (10 mL), after which cyclohexene (2.64 mL, 26 mmol) was gradually added. A white suspension soon appeared and the mixture was stirred for 2 h at 0-5°C. The system was connected to an azotometer; then a solution of 1-diazo-2-heptanone (1.40 g, 10 mmol) in THF (10 mL) was slowly added at 5-7°C. The resulting mixture turned deep red (homogeneous solution), while nitrogen evolved in approximately 90% yield. The methylating reagent (10 mmol) was added in DMSO (15 mL) and the resulting heterogeneous mixture was stirred overnight. It was then poured into ice-water (100 mL) and extracted with pentane (100 mL). The organic layer was washed twice with water (ca. 20 mL), dried over $MgSO_4$, and condensed at atmospheric pressure. In all cases, GLC analysis (5 ft x 1/8 in, 10% QF-1) showed the presence of very complicated mixtures, which appeared very similar. Although traces of 2-heptanone were present, octanones could not be detected by GLC-mass spectrometry.

Benzylation of Diethyl(3-nonen-4-yloxy)borane in the Presence of Potassium Fluoride and 18-Crown-6. A solution of 1-diazo-2-heptanone (0.77 g, 5.5 mmol) in THF (15 mL) was gradually added to triethylborane (0.87 mL, 6.0 mmol) in THF (5 mL) at 5-10°C. After nitrogen had evolved (ca. 95% yield), benzyl bromide (0.70 mL, 5.8 mmol), KF (1.82 g, 30 mmol) and 18-crown-6 (2.70 g, 10 mmol) were added in THF (20 mL). The flask was then warmed to room temperature and stirred for 4 h and subsequently refluxed for 3 h. The reaction mixture was then cooled (15°C), hydrolyzed with water (20 mL), then 1,4-dimethoxy-benzene (0.6358 g, 4.6 mmol) was added as an internal NMR standard. The crude mixture was extracted with pentane (200 mL). The organic phase was washed with water (2 x 30 mL), dried over $MgSO_4$ and condensed by distillation. Analysis

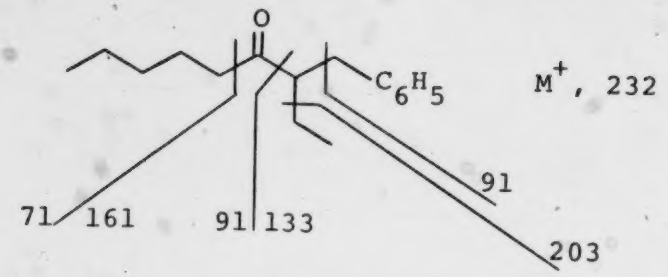
(NMR) showed the presence of benzylated ketone (2.4 mmol), formed in 44% yield, and benzyl bromide (3.4 mmol). ^{1}H NMR ($CDCl_3$, TMS), for benzyl bromide: δ 7.25 (broad s, 5H), 4.36 (s, 2H), for benzyl ketone: δ 7.13 (broad s) and for 1,4-dimethoxybenzene: δ 6.75 (s, 4H) and 3.61 (s, 6H).

The reaction was repeated in THF at reflux and the product ratio was analyzed at different intervals by NMR spectroscopy as shown in Table XVIII.

The product was isolated by column chromatography (silica gel, 15% CH_2Cl_2 in Skelly B), followed by Kugelrohr distillation to give 3-benzyl-4-nonanone as a colourless liquid: bp 100°C (0.02 mm Hg). GLC mass spectral analysis (10% SE-52 showed the single product peak to be uniform, and the fragmentation pattern was in agreement with the assigned structure. However, it was not possible to prove the absence of the regioisomeric 5-benzyl-4-nonanone; IR (neat): 1710 (s), 1610 (w), 1500 (w), 750 (s), and 710 cm^{-1} (s); ^{1}H NMR (CCl_4, TMS): δ 7.1 (broad s, 5H) phenyl, 2.9-1.9 (m, 5H) $C_6H_5C\underline{\underline{H}}_2C\underline{\underline{H}}COC\underline{\underline{H}}_2$, and 1.9-0.9 (m, 14H) C(1), C(2), C(6), C(7), C(8) and C(9) $C\underline{\underline{H}}_2$ and $C\underline{\underline{H}}_3$; MS m/e: 232 (15.53) M$^+$, 203 (39.09), 161 (23.26), 133 (18.53), 117 (8.60), 99 (36.07), 91 (100) and 71 (24.25), which has been rationalized according to Scheme XXXIX.

Mass measurement m/e, Calcd for $C_{16}H_{24}O$: 232.1827. Found: 232.1821.

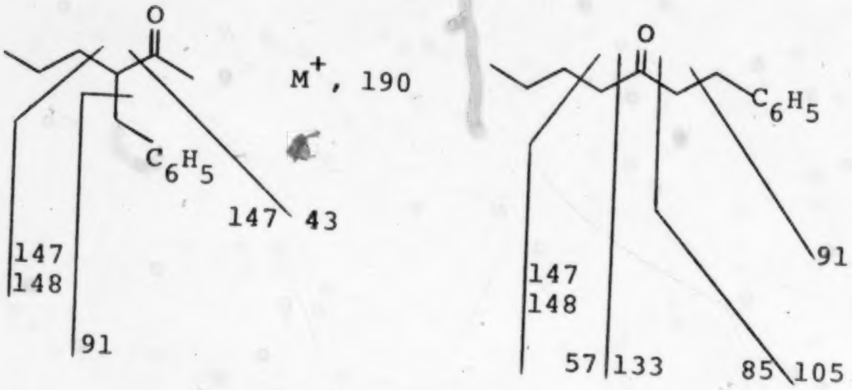
Scheme XXXIX



Benzylation of Diethyl(2-hexen-2-yloxy)borane in the Presence of Potassium Fluoride and 18-Crown-6. A solution of methyl vinyl ketone (3.40 mL, 42 mmol) in THF (20 mL) was added to triethylborane (3.94 mL, 28 mmol) in THF (20 mL). (The methyl vinyl ketone was dried over $CaCl_2$ and freshly distilled prior to use). The reaction mixture was stirred at 40°C for 2 h. After cooling to ca. 10°C, benzyl bromide (4.2 mL, 35 mmol), potassium fluoride (2.0 g, 30 mmol), and 18-crown-6 (1.86 g, 7 mmol) were added, and the resulting mixture was stirred for 7 h at room temperature. The mixture was then quenched with water and oxidized with hydrogen peroxide (30%) in aqueous sodium acetate (3 N), after which pentane (200 mL) was added. The organic layer was washed with water (2 x 20 mL), dried over $MgSO_4$ and condensed in vacuo. Column chromatography (silica gel, 15% CH_2Cl_2 in Skelly B) afforded the benzylated hexanones in 33% yield. Analysis by

GLC mass spectrometry (20% DEGS, 90-190°C) indicated the presence of 3-benzyl-2-hexanone and 1-phenyl-3-heptanone in a ratio of 94:6. 3-Benzyl-2-hexanone eluted first[110], MS m/e: 190 (6.2) M^+, 148 (19.1), 147 (58.8), 105 (9.0), 92 (9.6), 91 (100), 77 (7.3), 65 (15.0) and 43 (83.3), followed by 1-phenyl-3-heptanone: MS m/e, 190 (14.4), 148 (12.6), 147 (8.3), 133 (19.0), 130 (14.6), 106 (6.1), 105 (64.4), 104 (13.3), 91 (100), 85 (32.6), 77 (25.9), 65 (19.2), 57 (61.9), 43 (41.8) and 41 (43.0). The results may be rationalized as shown in Scheme XXXX.

Scheme XXXX

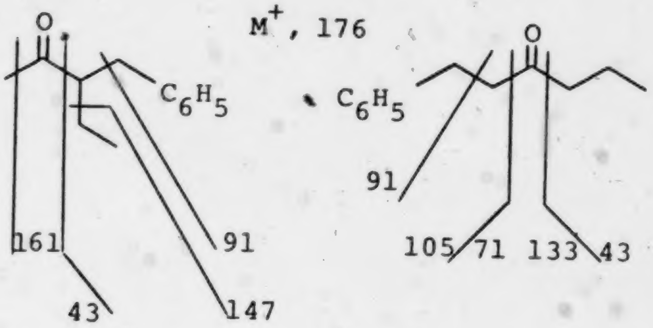


Benzylation of Diethyl (2-penten-2-yloxy)borane in the Presence of Lithium Methoxide. A solution of diazoacetone (0.42 g, 5.0 mmol) in THF (10 mL) was gradually added to triethylborane (0.85 mL, 6.0 mmol) at 5-10°C. Nitrogen evolution was ca. quantitative.

In a second flask, a suspension of lithium methoxide (11 mmol) in THF (10 mL) was prepared from methanol (0.44 mL, 11 mmol) and methyllithium (ca. 1.3 N), which could be followed by measuring the gas evolution. The enol borinate solution was then added to the suspension and the mixture was stirred for 30 min at ca. 5°C, after which benzyl bromide (0.72 mL, 6.0 mmol) was added. The mixture was stirred overnight at room temperature, then worked up as described above. Analysis by NMR spectroscopy indicated a 50% yield of benzylated 2-pentanones. GLC analysis (10% DEGS, 90-190°C programming) showed that 3-benzyl-2-pentanone and the undesired regioisomer were present in a 92:8 ratio; GLC MS m/e for 3-benzyl-2-pentanone: 176 (1.0) M^+, 161 (0.3), 147 (13), 91 (58), 65 (19) and 43 (100), and for 1-phenyl-3-hexanone: 176 (22) M^+, 133 (22), 105 (72), 91 (80), 71 (58) and 43 (100). These results can be rationalized according to Scheme XXXXI.

The addition of one equivalent of lithium methoxide resulted in only 30% of benzylated pentanones (ca. 2 h). Prolonged reaction time did not lead to increased yields (34% after 5 days). GLC analysis showed that the regioisomers were present in a ratio of 98:2 in favour of 3-benzyl-2-pentanone.

Scheme XXXXI



Synthesis of 3-Allyl-2-heptanone. An oven-dried 100 mL flask, equipped with stirring bar, addition funnel, thermometer, and septum inlet was flushed with nitrogen, flame-dried, and then connected to an azotometer. The flask was then charged with tributylborane (3.4 mL, 14.0 mmol) and THF (10 mL). To this was added a solution of diazoacetone (1.03 g, 12.2 mmol) in THF (10 mL) over a period of ca. 20 min, while the temperature was kept at 5-10°C. The reaction mixture was warmed to room temperature (quantitative N_2 evolution) and allyl bromide (3.6 mL, 42 mmol) was then added.

A second 100 mL flask was charged with 2-(dimethylamino)ethanol (1.40 mL, 14 mmol) in THF (10 mL) and a trace of triphenylmethane. Methyllithium (ca. 1.3 N) in ether was slowly added at 0-20°C (a white milky precipitate initially formed) until the red colour of triphenylmethane appeared. The flask was cooled to

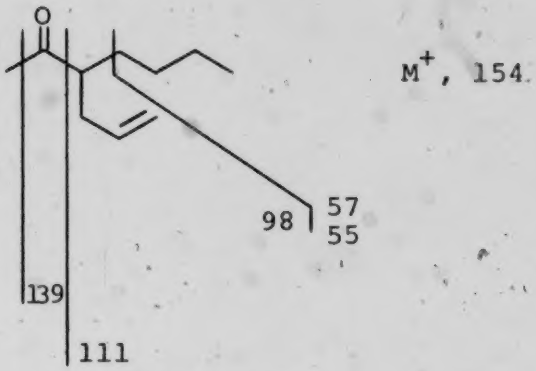
-78°C and the mixture of enol borinate and allyl bromide was added via a double-ended needle after which the cooling bath was removed. The reaction mixture was stirred for ca. 8 h at room temperature and then oxidized with 30% hydrogen peroxide (ca. 4 mL) and 3 N sodium acetate (20 mL). Pentane (250 mL) was added and the organic phase was washed with water (2 x 50 mL), dried over $MgSO_4$ and concentrated at atmospheric pressure. GLC analysis (20 ft x 1/8 in, 5% SE 30, 100° + 0.5°C/min) showed the presence of 75% 3-allyl-2-heptanone and 17% 2-heptanone. A pure sample of the alkylated product was obtained as a colourless liquid by preparative GLC (15% polyphenylether) and subsequent microdistillation: bp 100°C (18 mm Hg); IR (neat): 1715 (s), and 1640 cm^{-1} (m); ^1H NMR (CCl_4, TMS): δ 6.0-5.2 (m, 1H), 5.1 (m, 1H), 4.9 (m, 1H) $C\underline{\underline{H}}-C\underline{\underline{H}}_2$, 2.6-1.8 (m, 3H) $C\underline{\underline{H}}-C\underline{\underline{H}}_2-CH=CH_2$, 2.05 (s, 3H) $C\underline{\underline{H}}_3CO$, 1.7-1.1 (m, 6H) C(4), C(5) and C(6) $C\underline{\underline{H}}_2$, and 1.1-0.8 (broad t, 3H) $C\underline{\underline{H}}_3$; MS m/e: 139 (60), 125 (27), 111 (21), 109 (12), 98 (30), 97 (27), 85 (30), 83 (25), 81 (23), 71 (29), 69 (54), 67 (32), 57 (42) and 55 (100), which can be rationalized according to Scheme XXXXII.

Mass measurement m/e, Calcd for $C_9H_{15}O$ (M^+-Me): 139.1113. Found: 139.1118.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76.

Found: C, 77.61; H, 11.76.

Scheme XXXXII



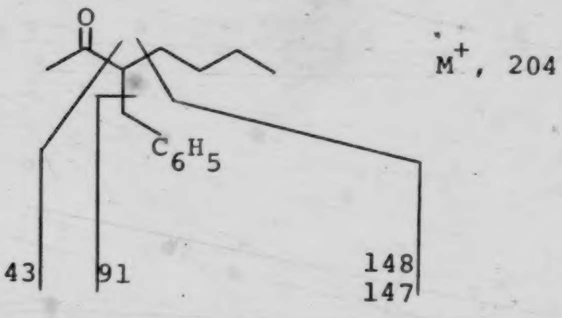
$$154 \xrightarrow[\text{-butene}]{\text{McLafferty}} 98 \xrightarrow{\text{-Me}} 83 \xrightarrow{\text{-CO}} 55$$

Synthesis of 3-Benzyl-2-heptanone. This was prepared as described above from diazoacetone (0.84 g, 10.0 mmol), tributylborane (2.65 mL, 11.0 mmol), 2-(dimethylamino)ethanol (1.0 mL, 10.0 mmol) and benzyl bromide (4.0 mL, 34 mmol). GLC analysis (10%, QF-1) showed the presence of a single isomer in 76% yield. This compound could be isolated as a colourless liquid in 70% yield by column chromatography (silica gel, first Skelly B, then CH_2Cl_2 gradient) and subsequent micro-distillation: bp 90°C (0.08 mm Hg); IR (neat): 1710 (s), 1605 (w), 1495 (w), 740 (s) and 700 cm^{-1} (s); ^1H NMR ($CDCl_3$, TMS): δ 7.3-6.9 (broad s, 5H) phenyl, 3.1-2.4 (m, 3H) $C_6H_5C\underline{\underline{H}}_2C\underline{\underline{H}}$, 1.9 (s, 3H) $C\underline{\underline{H}}_3CO$, and 1.7-

0.8 (m, 9H) C(4), C(5), C(6) and C(7) $C\underline{\underline{H}}_2$ and $C\underline{\underline{H}}_3$; MS m/e: 204 (7) M^+, 148 (25), 147 (66), 91 (100) and 43 (58), which may be rationalized as shown in Scheme XXXXIII.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87; O, 7.83. Found: C, 82.26; H, 9.88; O, 8.07.

Scheme XXXXIII



Synthesis of 3-Methyl-2-heptanone. This compound was prepared as described above from the reaction of diazoacetone (0.88 g, 10.5 mmol), tributylborane (2.88 mL, 12 mmol), 2-(dimethylamino)ethanol (1.2 mL, 12 mmol) and methyl iodide (2.5 mL, 40 mmol). GLC analysis (10 ft x 1/8 in Porapak Q, 230°C; 5 ft x 1/8 in 20% DEGS, 100°C) showed the presence of 3-methyl-2-heptanone (88%) as a single regioisomer, and 2-heptanone (11%). The major product was isolated by preparative GLC (15% polyphenylether), and possessed identical spectroscopic properties as those described in the literature[191]: IR (neat): 1710 cm^{-1} (s); ^1H NMR (CCl_4, TMS): δ 2.6-2.1

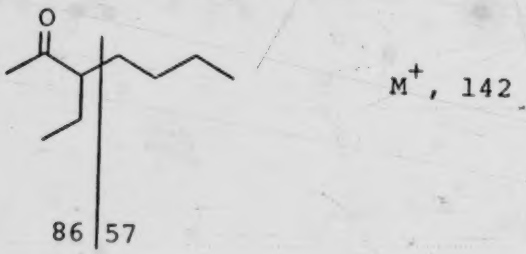
(m, 1H) C$\underline{\underline{H}}$CO, 2.05 (s, 3H) C$\underline{\underline{H}}_3$CO and 1.8-0.7 (m, 12H) hydrocarbon moiety with a doublet at 1.0 (J = 7 Hz) C$\underline{\underline{H}}_3$CH.

The analogous reaction, using dimethyl sulfate as the methylating reagent resulted in an 82% yield of 3-methyl-2-heptanone.

Synthesis of 3-Ethyl-2-heptanone. This compound was prepared as described above from the reaction of diazoacetone (0.30 g, 3.5 mmol), tributylborane (0.90 mL, 3.8 mmol), 2-(dimethylamino)ethanol (0.38 mL, 3.8 mmol) and ethyl iodide (0.80 mL, 10 mmol). The reaction yielded 3-ethyl-2-heptanone (49%) as a single regioisomer, and 2-heptanone (22%), as determined by GLC analysis (20 ft x 1/8 in, 5% SE-30, 100°C). The product was isolated by preparative GLC (Carbowax 6000, 90°C) and the spectroscopic data were identical to those reported in the literature[191]: IR (neat): 1715 cm^{-1} (s); ^{1}H NMR (CCl$_4$, TMS): δ 2.5-2.1 (m, 1H), C$\underline{\underline{H}}$CO, 2.01 (s, 3H) C$\underline{\underline{H}}$CO, 1.9-1.1 (m, 8H) C$\underline{\underline{H}}_2$, and 1.1-0.7 (overlapping t's, 6H) C$\underline{\underline{H}}_3$; MS m/e: 142 (7) M$^+$, 86 (95), 71 (33) and 57 (100), which may be rationalized as shown in Scheme XXXIV.

Mass measurement m/e, Calcd for C$_9$H$_{18}$O: 142.1357. Found: 142.1355.

Scheme XXXXIV



$$142 \xrightarrow[\text{- butene}]{\text{McLafferty rearr.}} 86 \xrightarrow{\text{-Me}} 71$$

Attempted Benzylation of Dicyclohexyl(1-hepten-2-yloxy)borane in the Presence of Lithium 2-(Dimethylamino)ethanol. A 100 mL flask was placed in an ice-bath and charged with borane-methyl sulfide complex (2.1 mL, 21 mmol) and THF (10 mL). Then cyclohexene (4.3 mL, 42 mmol) was slowly introduced by syringe at 0-10°C. A white precipitate soon appeared and the reaction was stirred for 2 h. The flask was then evacuated (0.01 mm Hg, 1h) to remove dimethyl sulfide, and subsequently filled with nitrogen, followed by addition of THF (30 mL). After cooling the flask in an ice-bath, 1-diazo-2-heptanone (2.80 g, 20 mmol) was gradually added at 5-7°C. Nitrogen evolved in ca. 90% yield. Benzyl bromide (4.8 mL, 40 mmol) was then added at -5°C.

A second 100 mL flask was charged with 2-(dimethylamino)ethanol (2.1 mL, 21 mmol), THF (20 mL) and a trace of triphenylmethane. Methyllithium (ca. 1.3 N) in ether was gradually added at 10°C until the red colour of triphenylmethide appeared. The suspension was cooled to -78°C and the mixture of enol borinate and benzyl bromide was transferred via a double-ended needle. The reaction mixture was slowly warmed and stirred overnight at ca. 10°C. By this time the colour had changed from its initial red-brown to black and a precipitate had formed. The resulting mixture was oxidized with 30% hydrogen peroxide (ca. 5 mL) and 3 N sodium acetate (ca. 30 mL) at ca. 25°C, followed by extraction with pentane (500 mL). The organic layer was washed successively with water, 1.5 N aq. HCl, water, 5% aq $NaHCO_3$, water, then dried over $MgSO_4$ and condensed under reduced pressure. The brown, oily crude residue was partially purified by column chromatography (silica gel, Skelly B, then 25% CH_2Cl_2 in Skelly B). Unreacted benzyl bromide eluted first, followed by the benzylated 2-heptanones (0.7 g, ca. 15% yield) GLC analysis (5% SE-30, 200°C) showed the presence of 1-phenyl-3-octanone and the isomeric 3-benzyl-2-heptanone in a ratio of 26:74; GLC MS (m/e) for 1-phenyl-3-octanone: 204 (12) M^+, 148 (21), 133 (30), 130 (21), 105 (73), 104 (21), 99 (34), 91 (100), 71 (29) and 43 (64); and for 3-benzyl-2-heptanone: 204 (4) M^+, 148 (30), 147 (80), 139 (30), 91 (100) and 43 (52). These fragmentation patterns can be rationalized in an analogous manner as those in Schemes XXXXI and XXXXIII.

Benzylation of the Lithium Enolates of 2-Heptanone with 2-(Diethylamino)ethyl Dicyclohexylborinate as Additive. 2-(Dimethylamino)ethanol (2.2 mL, 22 mmol) was added at 0°C to a white suspension of dicyclohexylborane (22 mmol) in 20 mL THF (prepared as described above). The suspension disappeared, while hydrogen evolved in quantitative yield. The resulting solution was gradually warmed to room temperature and the by-product, dimethyl sulfide, was removed by evacuation.

A solution of lithium diisopropylamide was prepared by addition of n-butyllithium (22 mmol) in hexane to diisopropylamine (5.0 mL, 36 mmol) in THF (30 mL) at -78°C. (A catalytic amount (ca. 10 mg) of 2,2-biquinoline was also added). 2-Heptanone (3.1 mL, 22 mmol) in THF (10 mL) was slowly added over a period of 1 h after which the solution was still purple (indicating an excess of base). The borinate was then transferred via a double-ended needle and the reaction mixture was warmed to 10°C (purple colour persisted). Benzyl bromide (5.0 mL, 42 mmol) was injected after ca. 30 min and the resulting solution was stirred for 2 h at 10°C, then 14 h at room temperature. The reaction mixture was worked up as described previously and column chromatography (silica gel, Skelly B; then

25% CH_2Cl_2 in Skelly B) afforded a mixture of benzylated 2-heptanones in ca. 30% yield (as measured by NMR spectroscopy). GLC analysis showed the presence of 1-phenyl-3-octanone and 3-benzyl-2-heptanone in a ratio of 16:84.

The lithium enolate of 2-heptanone could also be prepared by cleavage of the corresponding enol silyl ethers. The terminal enol silyl ether derivative was prepared in 86% regioselectivity by the method of House and coworkers[9] (in THF). GLC mass spectroscopy (20 ft x 1/8 in 5% SE-30, 80°C) and NMR analysis corroborated that the mixture of enol silyl ethers contained 86% of the terminal and 14% of the internal isomer. This enol silyl ether mixture was converted to the corresponding mixture of lithium enolates by treatment with methyllithium at room temperature (triphenylmethane as indicator)[9], which was then benzylated in the same manner as described in the previous experiment. This afforded a mixture of 1-phenyl-3-octanone and 3-benzyl-2-heptanone (ca. 30%) in a ratio of 8:92, in which the undesired isomer was the minor component.

Reaction of Tributylborane with Methyl Vinyl Ketone. An oven-dried 100 mL flask, equipped with a magnetic stirring bar, addition funnel and septum inlet, was charged with tributylborane (5.0 mL, 20.8 mmol) in

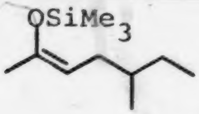
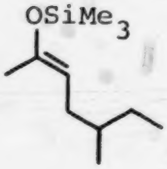
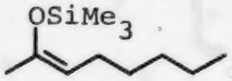
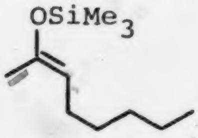
15 mL of THF. A solution of methyl vinyl ketone (2.5 mL, 30 mmol) in THF (15 mL) was gradually added at 25°C. An exothermic reaction occurred and the temperature rose to ca. 40°C, at which it was kept for another 1.5 h. The contents of the flask were then brought to room temperature and the septa were replaced by glass stoppers. The solvent was removed in vacuo and the resulting viscous liquid was distilled to give a mixture of enol borinates (ca. quantitative, no residue) as a colourless liquid: bp 90°C (0.01 mm Hg). This mixture was transferred as a 50% solution in d^8-toluene to ^{13}C and ^1H NMR tubes via a double-ended needle and these samples were sealed under vacuum: ^1H NMR (C_6H_6): δ 4.67 (tq, J = 7.5, J ≃ 1 Hz, 0.4H) E-vinylic H; 4.55 (tq, J = 7.0, J ≃ 1 Hz, 0.6H) Z-vinylic H; 2.1-1.8 (m, 2H) $C\underline{\underline{H}}_2C=$; 1.76-1.66 (m, 3H) $C\underline{\underline{H}}_3C=$; 1.6-1.1 (m, 14H) C(5), C(6), C(7), C(10), and C(11) $C\underline{\underline{H}}_2$, 1.1-0.7 (m, 13H) C(9) $C\underline{\underline{H}}_2$, and C(8) and C(12) $C\underline{\underline{H}}_3$; ^{13}C NMR (C_6H_6): δ 148.4 (66, 2 peaks) C(2), 111.4 (170) E-C(3), 110.1 (314) Z-C(3), 32.1 (267), 31.9 (202), 30.3 (189), 29.7 (256), 27.3 (242), 26.9 (645), 26.3 (751), 25.9 (296), 23.0 (385), 22.2 (275), 20.4 (64), 17.2 (123), and 14.2 (1113).

Reaction of (Z/E)-Dibutyl(2-octen-2-yloxy)borane with N-Trimethylsilylimidazole. The mixture of enol borinates was prepared as described above from tributylborane (7.2 mL, 30 mmol) and methyl vinyl ketone (4.0 mL, 50 mmol) in 30 mL of THF. The solvent was then removed in vacuo at room temperature. N-Trimethylsilylimidazole (4.40 mL, 30 mmol) - obtained from Aldrich Chemicals and used without prior purification - was then gradually added as a solution in 15 mL of THF at room temperature. An exothermic reaction occurred and the temperature of the reaction mixture increased to ca. 40°C. The solution was then stirred at room temperature for 1 h; distillation afforded 5.2 g of a mixture of enol silyl ethers (87%) as a colourless liquid: bp 85°C (20 mm Hg): IR (neat): 1670 cm^{-1} (broad) ^1H NMR (C_6H_6): δ 4.62 (t, J = 6.7 Hz, 0.4 H) E-vinylic H, 4.40 (t, J = 6.4 Hz, 0.6H) Z-vinylic H; 2.2-1.9 (m, 2H) $C\underline{\underline{H}}_2C=$, 1.76, 1.71 (s, 3H) Z- and E-$C\underline{\underline{H}}_3$-C=, 1.6-1.2 (m, 6H) C(5), C(6) and C(7) $C\underline{\underline{H}}_2$, 1.1-0.8 (m, 3H) C(8) $C\underline{\underline{H}}_3$, 0.20 (s, 9H) $(C\underline{\underline{H}}_3)_3Si$.

The mixture of enol trimethylsilyl ethers was analyzed by GLC mass spectrometry (5% SE-30, 20 ft x 1/8 in, 100°C) and the results are shown in Table XXII.

Synthesis of (E)-Dibutyl(2-hepten-2-yloxy)borane. An oven-dried 100 mL flask equipped with a magnetic stirring bar, addition funnel, and septum inlet, then charged with tributylborane (2.6 mL, 10.5 mmol) and THF (10 mL) and connected to an azotometer. A solution

Table XXII. GLC Mass Spectrometric Analysis of the Trimethylsilyl Enol Ether Derivatives (Eq. 90)

structure[a]	retention time (min)	composition (%)	fragmentation peaks, m/e
	31.6	7	200(3.8)M^+ 185(3.8), 144(10), 143(71), 130(6), 75(24), 73(100), 45(16), 43(18).
	35.0	5	200(4.1) M^+, 185(3.7), 144(10), 143(79), 130(4), 75(23), 73(100), 45(15), 43(19).
	38.8	57	200(6.6) M^+, 185(6.0), 157(6), 144(10), 143(68), 130(20), 115(17), 75(36), 73(100), 58(17), 45(17), 43(27).
	42.0	31	200(7.3) M^+, 185(5.4), 144(11), 143(82), 130(11), 115(6), 75(29), 73(100), 45(16), 43(14).

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[a] Structure assignment is based on ^{1}H and ^{13}C NMR data and on the sequence of elution (ref. 9).

of diazoacetone (0.84 g, 10.0 mmol) in THF (10 mL) was gradually added at 5-10°C and nitrogen evolved in quantitative yield. The addition funnel and septa were replaced by a distillation apparatus and glass stoppers under a continuous flow of nitrogen. The solvent was removed by distillation (atm. press.), and the residue was distilled under reduced pressure to give the enol borinate as a colourless liquid in ca. quantitative yield: bp 150°C (0.005 mm Hg); ^{1}H NMR (ext. TMS): δ 4.45 (tq, J = 7.5, J = 1 Hz, 1H) C$\underline{\underline{H}}$=, 2.0-1.7 (m, 2H) C$\underline{\underline{H}}_2$C=, 1.58 (d, J = 1 Hz, 3H) C$\underline{\underline{H}}_3$C=, 1.5-0.5 (m, 25H) hydrocarbon envelope; ^{13}C NMR (ext CDCl$_3$, TMS): δ 147.9 (132) C(2), 110.3 (365) C(3), 32.1 (264), 26.3 (288), 26.1 (375), 25.4 (448), 25.1 (56), 22.0 (50), 21.8 (261), 19.5 (52), 16.4 (204), 13.4 (562) and 13.3 (348).

Synthesis of (E)-Trimethyl(2-hepten-2-yloxy)silane.

An oven-dried 100 mL flask, equipped with a magnetic stirring bar, addition funnel and septum inlet, was charged with tributylborane (5.5 mL, 23 mmol) and THF (20 mL), then connected to an azotometer. A solution of diazoacetone (1.82 g, 21.6 mmol) in THF (20 mL) was gradually added over 20 min and nitrogen evolved in quantitative yield (98%). The nearly colourless reaction mixture was warmed to room temperature (0.5 h) and then cooled to -78°C. N-Trimethylsilylimidazole

(3.4 mL, 23 mmol) was injected, then the cooling bath was removed and the mixture was stirred overnight at ambient temperature. The solvent was then removed by distillation at atmospheric pressure. The flask was evacuated (< 0.01 mm Hg) and the enol silyl ether was trapped at -78°C. The distillate was dissolved in pentane (100 mL) and the organic phase was washed with ice cold 5% $NaHCO_3$ (20 mL), water (2 x 20 mL), then dried over $MgSO_4$. Removal of solvent at atmospheric pressure provided 3.2 g of the enol silyl ether (80%) as a colourless liquid. GLC analysis (5% SE-30, 20 ft x 1/8 in, 80°C) showed that the E-isomer (retention time: 48.0 min) was the sole product - none of the Z-isomer (retn. time: 43.5 min)* could be detected. The spectroscopic properties were identical to those reported earlier[9]: IR (neat) 1665 cm^{-1}; ^{1}H NMR (ext. TMS): δ 4.50 (t, J = 7.5 Hz, 1H) $C\underline{\underline{H}}=$; 2.0-1.8 (m, 2H) $C\underline{\underline{H}}_2C=$; 1.67 (s, 3H) $C\underline{\underline{H}}_3-C=$; 1.4-1.1 (m, 4H) C(5) and C(6) $C\underline{\underline{H}}_2$; 1.1-0.8 (m, 3H) C(7) $C\underline{\underline{H}}_3$ and 0.13 (s, 9H) $(C\underline{\underline{H}}_3)_3Si$.

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* A mixture of trimethyl(1-hepten-2-yloxy)silane and (Z)- and (E)-trimethyl(2-hepten-2-yloxy)silane prepared via a different route[9] had the following retention times on this particular column: 42.0, 43.5 and 48.0 min, respectively.

Thermal Equilibration of (E)-Dibutyl(2-hepten-2-yloxy)borane. A 50% solution of the pure E-isomer in d^8-toluene was sealed in ^{1}H and ^{13}C NMR tubes, and heated for 24 h at 100°C; ^{1}H NMR, 200 MHz (ext. TMS): δ 4.52 (tq, J = 7.8 Hz, J = 1 Hz, 0.8 H) E-C$\underline{\underline{H}}$=, 4.39 (tq, J = 7.2, J = 1 Hz, 0.2H) Z-C$\underline{\underline{H}}$=, 1.9-1.6 (m, 2H) C$\underline{\underline{H}}_2$-C=, 1.55 (d, J = 1 Hz, ~ 0.6H) Z-C$\underline{\underline{H}}_3$C=, 1.52 (d, J = 1 Hz, ~ 2.4 H) E-C$\underline{\underline{H}}_3$C=, 1.4-1.0 (m, 12H) C(5), C(6), C(9) and C(10) C$\underline{\underline{H}}_2$ and 0.9-0.6 (m, 13H), C(8) C$\underline{\underline{H}}_2$, and C(7) and C(11) C$\underline{\underline{H}}_3$.

The samples were subsequently heated again for a total of 64 h at 100°C: ^{1}H NMR spectral data, did now show a 3:2 ratio of stereoisomers in favour of E-isomer; ^{13}C NMR: δ 147.8 (117) E-C(2), 147.5 (95) Z-C(2), 110.4 (261) E-C(3), 109.2 (173) Z-C(3), 31.9 (215), 31.3 (165), 26.2 (328), 26.1 (542), 26.0 (501), 25.9 (203), 25.4 (643), 25.1 (130), 24.7 (192), 21.9 (181), 21.8 (243), 21.4 (153), 16.3 (160), 13.4 (751) and 13.2 (416).

The solution was then heated at 140°C. After 40 h the ^{1}H NMR spectral data showed a 3:7 ratio of E- and Z-stereoisomers. Further heating did not result in any change of this ratio: ^{1}H NMR, 90 MHz: δ 4.50 (0.3H), 4.35 (0.7H), 1.9-1.6 (m, 2H), 1.6-1.5 (m, 3H), 1.4-1.0 (m, 12H) and 1.0-0.6 (m, 13H).

Synthesis of (E)-Dibutyl(5-undecen-6-yloxy)borane. An oven-dried 100 mL flask, equipped with a magnetic stirring bar, addition funnel, and septum inlet, was charged with tributylborane (2.40 mL, 10 mmol) and THF (10 mL) and then connected to an azotometer. A solution of 1-diazo-2-heptanone (1.40 g, 10 mmol) in THF (10 mL) was gradually added at 5-10°C and nitrogen evolved in quantitative yield. The solvent was removed at room temperature under reduced pressure and the nearly colourless liquid was kept at 50°C for 1 h under high vacuum (< 0.01 mm Hg). The contents of the flask were cooled to 0°C and 2 mL of d^8-toluene was added.

This solution was transferred to ^{1}H and ^{13}C NMR tubes which were subsequently sealed off under vacuum. NMR spectral data showed the formation of stereoisomerically pure (E)-dibutyl(5-undecen-6-yloxy)borane: ^{1}H NMR: δ 4.64 (t, J = 7.5 Hz, 1H) E-vinylic H, 2.09 (t, J = 7.0 Hz, 2H) C(7) $C\underline{\underline{H}}_2$, 1.95 (tt, J = 7.5, J = 7.5 Hz, 2H) C(4) $C\underline{\underline{H}}_2$, 1.6-1.1 (m, 18H) C(2), C(3), C(8), C(9), C(10), C(13) and C(14) $C\underline{\underline{H}}_2$ and 1.1-0.6 (m, 16H) C(12) $C\underline{\underline{H}}_2$, and C(1), C(11) and C(15) $C\underline{\underline{H}}_3$; ^{13}C NMR: δ 152.3 (120) C(6), 111.3 (415) C(5), 33.0 (416), 31.9 (477), 31.2 (472), 27.0 (839), 26.8 (582), 26.3 (729), 26.0 (84), 23.0 (462), 22.7 (402), 20.5 (85) and 14.2 (863).

After heating the sample to 100°C for 12 h, the

NMR spectrum showed no change. It was then heated for 70 h at 134°C. The colour of the solution remained virtually colourless and the NMR spectrum showed that now the Z-isomer was exclusively present, ^{1}H NMR, 90 MHz: δ 4.53 (t, J = 7.4 Hz, 1H) Z-vinylic H, 2.3-1.7 (m, 4H) C(4) and C(7) $C\underline{\underline{H}}_2$, 1.7-1.2 (m, 18H) C(2), C(3), C(8), C(9), C(10), C(13) and C(14) $C\underline{\underline{H}}_2$, and 1.2-0.8 (m, 16H) C(12) $C\underline{\underline{H}}_2$ and C(1), C(11) and C(15) $C\underline{\underline{H}}_3$.

An aliquot of the pure (E)-dibutyl(5-undecen-6-yloxy)borane was heated for ca. 20 h at 135°C. After cooling to room temperature, the sample was quenched with N-trimethylsilylimidazole. The resulting mixture (ca. 1:1) of (E/Z)-enol silyl ethers was purified by preparative GLC (15% Polyphenyl ether, 100°C): ^{1}H NMR (CCl_4): 4.42 (t, J = 7.5 Hz, ~ 0.5H) E-vinylic H, 4.31 (t, J = 7 Hz, ~0.5H) Z-vinylic H, 2.1-1.8 (m, 2H) C(4) and C(7) $C\underline{\underline{H}}_2$, 1.6-1.2 (m, 10H) C(2), C(3), C(7), C(8) and C(9) $C\underline{\underline{H}}_2$, 1.0-0.8 (m, 6H) C(1) and C(10) $C\underline{\underline{H}}_3$, and 0.16 (s, 9H) $(C\underline{\underline{H}}_3)_3Si$.

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